Extracorporeal Circulation

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EXTRACORPOREAL CIRCULATION

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PREFACE

THE DEVELOPMENT of extracorporeal circulation has been the product of work in many laboratories both in this country and abroad Tracing back to the pioneering work in this imaginative and difficult field it has followed the course so characteristic of many scientific and surgical advances After many years of slow growth groping for solutions to important practical problems extracorporeal circulation has suddenly blossomed into a technique now widely used to bring relief to patients suffering from heart disease It is not difficult to foresee that techniques of this type may be used for the support of acute and chronic circulatory illness and as ancillary methods in other surgical problems such as cancer surgery and organ transplantation

A sizeable fraction of this development has been supported through appropriations voted by the Congress and allotted to the United States Public Health Service for expenditure through the National Institutes of Health The research is most clearly oriented towards the treatment of heart disease and for this reason most of these funds have flowed through the National Heart Institute The National Advisory Heart Council, as the senior policy making group of the National Heart Institute has maintained a consistent and enthusiastic interest in the development of extracorporeal circulation. In the early spring of 1957 it was their suggestion that a conference be held to discuss developments in this field.

Recommendations for research grants in this field have come through the Surgery Study Section of the National Institutes of Health because much of the research in this field was underway in departments of surgery and the practical application of extracorporeal circulation would be largely in the hands of surgeons It was therefore appropriate that the Surgery Study Section be designated to arrange this conference This group of surgeons in its regular meetings has made recommendations concerning a large number of proposals pertaining to this field

It was our intent to hold a conference big enough to include those many individuals who have made contributions in this field. It was our desire that all individuals be invited who were working in this field with the support of the United States Public Health Service. At the same time, it was clearly to the advantage of the group to limit the size of the meeting in order to achieve the freedom of discussion that was deemed essential to its success. Also, it was our specific purpose after the meeting to draw up a brief statement as to future developments and lines of investigation which should be supported and fostered, and to publish the proceedings.

Accordingly the plans of the meeting were drawn together. A site was selected at the Edgewater Beach Hotel in Chicago. The program was drawn up and the meeting was convened on September 20, 1957, at noon.

This book brings together the formal papers and the informal discussion presented at that meeting. It was thought to be important to prepare this book with maximum speed. For this reason there has not been the usual opportunity for the authors to review their galley proofs. Manuscripts, illustrations and discussions have been prepared, printed and proofread in page form. We are indebted to all the authors and discussers for making possible this short-cut which puts the book into the hands of the reader much sooner than otherwise would have been possible. None had the opportunity to read proof on discussions. For this reason, errors may be present that otherwise would be avoided, but it is hoped that early production of these Proceedings will compensate for the errors that have escaped detection.

An important aspect of the approach to this problem has been our complete freedom of scientific endeavor. This has expressed itself both in the wide geographical distribution of workers and in the varied nature of the biological approaches being used. Any sort of standardization of equipment or of research design would therefore be most unfortunate. On the other hand, an immediate outgrowth of the meeting was the realization of a need for common modes of measurement, a common terminology and common points of reference for the development of apparatus and technique in extracorporeal circulation. For this reason, a committee

was appointed with Dr Frank Gerbode as Chairman to investigate the codification of expressions methods of comparison terms of measurement and standards of performance It is with pleasure and with gratitude to this committee that we are able to include their report in this volume

The Surgery Study Section and its Subcommittee on the Conference wish to acknowledge their debt of gratitude to those many people who have made this venture possible Dr Harris Levin and Dr Jack Milder as Executive Secretaries of the Surgery Study Section have carried out the great bulk of formal arrangements with the able secretarial assistance of Mrs Anna Marie Perrell and of Miss Reecie Hodgson secretary to Dr J Garrott Allen We are indebted to Mr James B Glaze Photographer University of Chicago for the long and tedious hours entailed in the prompt photographic reproduction of the 83 illustrations prepared from the slides employed by the discussants Thus the reader has available nearly all illustrations used and each has been keyed to the discussion We are indebted to Mr A E Wright for the excellence of the arrangements at the hotel and to Mr Warren Green of Charles C Thomas Publisher who has made the rapid publication of this book possible We wish to express deep appreciation to Dr George H A Clowes Dr John W Kirklin and Dr C Walton Lillehei who advised the Committee on Arrangements Most especially all of us on the Surgery Study Section as well as the participants in the Conference wish to express our gratitude to the Subcommittee who organized the meeting and the program and to Dr J Garrott Allen of the University of Chicago who carried out the local arrangements and who has taken on the tremendous task of editing this book with such energy speed and effectiveness

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FOREWORD

By

DR JAMES WATT

Director, National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare

THE NATIONAL HEART INSTITUTE and the National Advisory Heart Council cordially welcome you and hope that each of you will find the conference enduringly profitable pleasurable and memorable

I regard it as a privilege to be able to participate in the initial event of this conference for I believe that this is an historical occasion of unusual moment Obviously the very fact of scientists of the calibre of those present gathering here to exchange and to yield the products of their thinking and experience is itself a noteworthy event

But I feel that this conference may be especially significant for still another reason To me it signalizes a time of harvest The seeds planted by physiologists experimenting in the perfusion of isolated organs before the turn of the century are now bearing a rich crop of fruit in the form of clinically useful tools and technics for the maintenance of extracorporeal circulation

As you know this growth has not been continuous but intermittent and paced by other advances in the repair of cardiac defects that have demanded the suspension of heart action for longer and longer periods of time The fact that progress in cardiac surgery has been greatly dependent on advances in extracorporeal circulation has long been recognized by surgeons everywhere In the 1930s when this dependence became acutely apparent Laurence O Shaughnessy of the Lambeth Cardiovascular Clinic in London wrote in *The Lancet* " the real key to further advance in the surgical treatment of established cardiac defects

will only be provided by the provision of some simple and efficient method of maintaining cerebral circulation while the heart is temporarily out of commission. Naturally there are many other problems of local nature for solution . . . but, so long as the surgeon is faced with the certainty of irreparable cerebral damage if he interrupts the circulation for any appreciable period, he has little incentive to devise operative procedures that can never be carried out."

It has been largely this need, expressed by Major O'Shaughnessy two decades ago, that has impelled the progress which has been made. This is especially true for the current decade, when advances in cardiac surgery have necessitated open access for many minutes to the chambers of the heart.

The National Advisory Heart Council has recognized since the earliest days of the Heart Institute's existence how dependent progress in the field of surgery has been on the development of ways of maintaining the circulation after exclusion of the heart.

By September of 1949, when the Heart Institute was only a little over a year old, the Council had already approved more than $100,000 for the support of several research projects to attack this problem under the direction of some of the country's most capable investigators in this area of research. We have already made profits on this investment and the returns are still coming in. The profits I refer to are the people happily alive and healthy, because of the reparative work done with the help of these machines and methods developed from this and related work.

The interest of the Heart Institute in this problem has continued to grow in pace with the demands of surgeons for its solution. In the past ten years—the decade of greatest need, as well as greatest progress in this area—the Council has recommended the expenditure of approximately two and a quarter million dollars for the support of more than fifty research projects in extracorporeal circulation. Those of us who are associated with the National Heart Institute take pride in being able to identify ourselves with the many scientists throughout the country who, with the aid of these grants, have contributed so much to the progress which has been made.

Obviously many important problems remain to be solved by continuing research in this area of cardiac surgery In the future as in the past progress in the surgical treatment of many of the heart defects that are now irreparable will continue to depend heavily on the development of better techniques and tools for extracorporeal circulation With this continuing need in mind the Council has already approved over $700 000 in grants for future use in research in extracorporeal circulation

Our current position in the history of extracorporeal circulation can perhaps be compared with the turn of the century in the history of automotive transportation We're off the ground now—we have apparatus that really works But it's still the era of the Pierce Arrow the Electric Brougham and the White Steamer Many divergent objectives and operating principles are being developed some of which will prove out in use and some of which will be discarded

One of the reasons we are meeting here this weekend is because we need better integration of these diverse ideas and objectives—the kind of integration that promotes clarity in thinking and more rapid taking of objectives It is the primary purpose of all scientific meetings to promote progress through the interchange of ideas and plans We learn to avoid the mistakes already made by others and equally important, to duplicate their successes Then too there is a synergistic effect from the interchange of widely differing patterns of thinking on the same subject in the genesis of new patterns of thinking new projects and new accomplishments This I think is the great profit of a really successful scientific meeting

If prophecy has a place in the equipment of scientists the scientific meeting is the place where it is most likely to manifest itself In meeting friends and colleagues with new and different ideas in discussing and planning the things that we find most exciting—the combination of social and intellectual stimulation we encounter under the circumstances is most likely to provide the flashes of insight by which we perceive the future possibilities of our science

I'm not a surgeon so I have no business waxing prophetic in the area of surgical science but it's obvious even to me that the

cardiac surgeon today is standing on a wonderfully optimistic historical vantage point. The view backward is one to inspire pride in the scientist who has been making contributions in the area of extracorporeal circulation, and the view ahead is surely one to fire the imagination of anyone who cares to look at the future of cardiovascular surgery.

PUMPS AND OXYGENATORS

SECTION I

CHARACTERISTICS OF AN IDEAL PUMP FOR EXTRACORPOREAL CIRCULATION

By

HENRY T BAHNSON, M D

It is with the proper sense of proportion that the Study Section has allotted to discussion of pumps the shortest of the various sessions as most people here are least dissatisfied with the pumping component of the extracorporeal circulation There is certainly less experimental data to compare different pumps and other problems of the extracorporeal circulation more urgently need solution On the other hand in the present imperfect state of our knowledge the pump is one component which can more completely benefit from modern engineering than other elements of the extracorporeal system if we can define the limiting factors and experimentally evaluate and establish the desired characteristics

Scores of pump designs are available many with the support of successful experimental and clinical use After using a roller pump satisfactorily in a number of instances we have questioned the need for departure from this basic design originated by DeBakey and developed to a high degree of excellence by Gibbon and his associates A feeling that a more intermittent type of pump should be carried to the same degree of excellence has largely motivated our efforts in the last several years to construct a similarly reliable and theoretically sound intermittent type pump Construction materials type of compression, and the mechanism of control play such an important role in the fabrication of pumps for extracorporeal circulation that comparison of pumps of different types is not possible from available information

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Aided by Grant H 1326 from the National Institutes of Health, U.S Public Health Service

I would like to discuss the hypothetical ideal pump under four headings, listing limiting factors and desirable features These are (1) the influence of restricted orifices, (2) the trauma of extracorporeal pumping, (3) the need for variable flow and automatic controls, and (4) measurement of pump output

First, restricted orifices must be interposed in both the venous and arterial lines connecting subject and pump These should be as wide and as short as possible but available techniques of cannulation require that some restriction be placed On the venous line this means that some form of aspiration has to be applied if central venous pressure in the subject is to remain normal The greater the resistance of the cannula and the higher the flow, the greater this aspiration must be Although gravity may be used for this purpose, a more readily regulated force seems desirable The restriction of venous cannulae and the force required to overcome this resistance have played a dominant role in flow through the extracorporeal circulation in our experience We have attempted to maintain central venous pressure nearly normal and use as large a venous cannula as possible, manually throttling venous flow if our gravity drainage becomes excessive Ideally this will be done automatically

Although cannulation of the aorta itself is possible, the easily available smaller vessels, such as the subclavian or femoral, require the presence of a restricted orifice in the arterial line also It follows that pressure in this arterial line must exceed that of the normal ventricle and correspond more to that proximal to a stenosed semilunar valve The effect of this pressure on pump output cannot be neglected, particularly in relation to calibration of flow

There must be little if any trauma, either chemical or physical, inflicted on the blood Material which contacts the blood must cause minimal chemical change, the most obvious evidence of chemical change being initiation of thrombosis Synthetic materials seem least damaging in this respect Design of the pump should be such that stagnation does not occur as even in the body stagnation breeds thrombosis The modern trend in blood perfusion equipment is towards expendable plastic material, and I believe this trend should be extended to an artificial heart We

have been so forcefully impressed with the difficulty of thorough cleaning of blood and protein from plastic and metallic parts that I feel sure the ideal pump chamber should not be reused

Physical trauma is also to be avoided Turbulence is usually listed as a principal offender in causing hemolysis but the mechanism is not clear Internal valves and abrupt changes in tubing diameter which might cause turbulence must be avoided Just as important may be avoidance of unwanted shock and high pressure waves which may cause damage by sudden positive or negative pressure This has been our principal objection to the popular Sigmamotor pump and possibly explains why it has in our experience been associated with more hemolysis than roller or intermittent pumps we have used

The most complex problem associated with a pump is that of flow control Continuously variable flow is required from zero to about 5 liters per minute and this flow must be susceptible to control Either stroke volume stroke rate or both might be altered to vary flow in the ideal pump Both are done in the body Just what should be the controlling parameter is not entirely clear Earlier systems maintained constant the volume of blood in the extracorporeal system Obviously the patient must not be bled or overtransfused Our clinical work indicates, however that if this control is simply of the volume of blood in the machine excessive flows will be obtained when the resting heart and lungs are emptied of blood during cardiotomy In some instances this volume may amount to more than a liter Probably the parameters which should be selected for control involve an integration of arterio-venous oxygen differences and arterial and venous pressures Servo mechanisms in the intact body incorporate all these factors in regulation of flow and pressure and our clinical perfusions have proceeded better when an effort was made to monitor these parameters and regulate flow and transfusion accordingly There is no question in my mind that in the ideal perfusion mean arterial and venous pressures and arterio-venous oxygen difference should remain unchanged

I am confident that regulation of the ideal pump must be automatic thus freeing the operator to monitor the extracorporeal circulation Because the regulating signal can be much stronger

I would like to discuss the hypothetical ideal pump under four headings, listing limiting factors and desirable features These are (1) the influence of restricted orifices, (2) the trauma of extracorporeal pumping, (3) the need for variable flow and automatic controls, and (4) measurement of pump output

First, restricted orifices must be interposed in both the venous and arterial lines connecting subject and pump These should be as wide and as short as possible but available techniques of cannulation require that some restriction be placed On the venous line this means that some form of aspiration has to be applied if central venous pressure in the subject is to remain normal The greater the resistance of the cannula and the higher the flow, the greater this aspiration must be Although gravity may be used for this purpose, a more readily regulated force seems desirable The restriction of venous cannulae and the force required to overcome this resistance have played a dominant role in flow through the extracorporeal circulation in our experience We have attempted to maintain central venous pressure nearly normal and use as large a venous cannula as possible, manually throttling venous flow if our gravity drainage becomes excessive Ideally this will be done automatically

Although cannulation of the aorta itself is possible, the easily available smaller vessels, such as the subclavian or femoral, require the presence of a restricted orifice in the arterial line also It follows that pressure in this arterial line must exceed that of the normal ventricle and correspond more to that proximal to a stenosed semilunar valve The effect of this pressure on pump output cannot be neglected, particularly in relation to calibration of flow

There must be little if any trauma, either chemical or physical, inflicted on the blood Material which contacts the blood must cause minimal chemical change, the most obvious evidence of chemical change being initiation of thrombosis Synthetic materials seem least damaging in this respect Design of the pump should be such that stagnation does not occur as even in the body stagnation breeds thrombosis The modern trend in blood perfusion equipment is towards expendable plastic material, and I believe this trend should be extended to an artificial heart We

have been so forcefully impressed with the difficulty of thorough cleaning of blood and protein from plastic and metallic parts that I feel sure the ideal pump chamber should not be reused

Physical trauma is also to be avoided Turbulence is usually listed as a principal offender in causing hemolysis but the mechanism is not clear Internal valves and abrupt changes in tubing diameter which might cause turbulence must be avoided Just as important may be avoidance of unwanted shock and high pressure waves which may cause damage by sudden positive or negative pressure This has been our principal objection to the popular Sigmamotor pump and possibly explains why it has in *our experience been associated with more hemolysis than roller* or intermittent pumps we have used

The most complex problem associated with a pump is that of flow control Continuously variable flow is required from zero to about 5 liters per minute and this flow must be susceptible to control Either stroke volume stroke rate or both might be altered to vary flow in the ideal pump Both are done in the body Just what should be the controlling parameter is not entirely clear Earlier systems mantained constant the volume of blood in the extracorporeal system Obviously the patient must not be bled or overtransfused Our clinical work indicates however that if this control is simply of the volume of blood in the machine excessive flows will be obtained when the resting heart and lungs are emptied of blood during cardiotomy In some instances this volume may amount to more than a liter Probably the parameters which should be selected for control involve an integration of arterio-venous oxygen differences and arterial and venous pressures Servo mechanisms in the intact body incorporate all these factors in regulation of flow and pressure and our clinical perfusions have proceeded better when an effort was made to monitor these parameters and regulate flow and transfusion accordingly There is no question in my mind that in the ideal perfusion mean arterial and venous pressures and arterio-venous oxygen difference should remain unchanged

I am confident that regulation of the ideal pump must be automatic thus freeing the operator to monitor the extracorporeal circulation Because the regulating signal can be much stronger

when levels of pressures are sensed in the extracorporeal system itself, this has usually been done and automatic controls have maintained constant the volume of blood in the extracorporeal system Although we would like to regulate automatically the extracorporeal system by venous and arterial pressure in the subject, the readily available signals from his vascular system require such amplification that the amplified signal has not been stable enough to use in the past In the ideal pump of the future this should be possible Although a simple automatic control is desirable, it seems unlikely that a system without any amplification will be the ideal

Finally, the ideal pump will be so constructed that an accurate measure of its output is available continuously Either a flowmeter must be incorporated or the effects of varying diastolic filling or systolic ejection pressures must be known Accurate calibration under reproducible conditions is of utmost importance in obtaining needed physiological data

After this brief listing of what I believe are desirable features in the pump of an extracorporeal circulation, I shall simply state that we have nearly finished a pump incorporating many of these features As a result of help from the National Institutes of Health we have benefited from the association of Mr John Edwards, an engineer, employed to construct a pump which might be used with various oxygenators Information gained from an earlier model of a pump of similar principle has been incorporated

An intermittent type of pump was selected because it had proven satisfactory in principle in an earlier model, and experiments by both Dennis and Melrose had shown this type of pump to be associated with less hemolysis than the roller type Since we have only recently begun to test this apparatus there is little to be gained by more description of it except that it is powered by an automatically controlled hydraulic system which imposes pressure in the pattern of a sine wave on a blood containing cylinder External valves, similarly powered hydraulically, constrict the tubing entering and leaving the chamber at the appropriate times Stroke to stroke control is achieved by a sensing device on a small closed reservoir so that stroke volume is made

to correspond to filling of the reservoir during the preceding stroke

In conclusion insufficient data are available to define completely the qualifications of an ideal extracorporeal pump Some of the presently limiting and desirable features can be listed, but available data are not adequate to establish one type of pump as ideal even in principle Questions which urgently need answers include What should be the controlling parameter for output of the pump? How automatic should the pump be? Which is preferable pulsatile or non pulsatile flows? It is hoped that the answers to these and other questions will be forthcoming in the next several days

The advice of my associates, notably Dr Frank C. Spencer and John F Edwards, has been helpful.

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Such are the meager materials available to judge this important question which surely merits close study at this time It is safe to say however that no refined mechanism to ape the normal pulse need be sought and that it is likely that considerable latitude in this matter exists

PUMP MECHANICS

Unhampered by exacting physiological criteria the factors underlying the choice of a pump are in essence practical ones Pumps can be divided into those designed to produce a continuous output and those whose action necessarily imparts a pulse This division is a fundamental and important one though in any particular instance it may be difficult to determine precisely in which category a pump belongs

Continuous flow pumps are in the main used to move large flows at low pressures The household fan the aeroplane airscrew the water pump in automobile cooling systems and the familiar boat propellers are all examples having in common an absence of valves to direct the flow of gas or fluid and depending for their pumping action on the rotation of a system of blades set at an angle about the axis of rotation The highest refinement of such a pump is the gas turbine or jet engine developing, as it does enormous power from the continuous movement of literally tons of air a minute

No adaptation of this type of pump seems to me to have any useful place in the development of heart lung machines While producing an inherently smooth flow with the advantage that such a flow encounters minimum resistance to its passage along tubes and through orifices it can only do this at the cost of many well nigh insuperable disadvantages Any form of rotating screw allows considerable "slip"—that is the rotating blades slide through the fluid pumped across its direction of flow This is merely a source of inefficiency in such applications as propelling a ship

CONTINUOUS AND PULSATILE FLOW PUMPS

By

DENIS MELROSE, M.D.

WERE there any really conclusive evidence as to the role of the pulse in the circulation of the blood our choice of a mechanical substitute for the heart would be made wholly on these grounds. However, as yet no such evidence is available and we are forced to a number of assumptions.

Pulsatile flow is the natural one and we must assume that the body is adapted to such a flow, though to argue from this that it is essential would be dangerous, for it is impossible to imagine any other biological solution. Certainly a wide variation in pulse pressure and contour is normal and reference to such cardiovascular malformations as coarctation of the aorta or aortic valvular incompetence indicate that the extremes of minimum and maximum pulse amplitudes are well tolerated. Whole body perfusions in animals, using non-pulsatile flows have been carried out successfully, as have a large number of perfusions in man where the flow has been only minimally pulsatile.

Recent experiments have cast doubt on earlier results of renal perfusion which had indicated that the pulse had a beneficial effect on the activity of the kidney. Neither Selkurt (1) nor Ritter (2) were able to demonstrate any significant alteration in renal function when pulsation was almost excluded from the arterial supply to the kidney without change of mean arterial pressure. These were, of course, short-term experiments and may have less validity over long periods. But even the most ambitious exponent of the heart-lung bypass must at present be concerned largely with such short term mechanisms.

That movement in general, and particularly the arterial pulse, is concerned in the dynamics of the lymph circulation is generally

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put of certain of them has often been regarded as continuous For convenience it is suggested that they be regarded as falling into two categories—those of high amplitude pulsation and those of low amplitude pulsation

In the first category are all those pumps in which blood is drawn into a container through a one way valve and then during the pumping phase is ejected through another one way valve The design of Dale and Schuster (5) in 1927 is perhaps the best known and serves as a pattern Variations on this theme are two numerous to detail but on this basic pattern can be elaborated mechanisms giving almost any desired characteristics of output save that of continuous flow though these pumps are usually of high amplitude pulse type A recent modification now employed in several machines allows a simple straight plastic tube to be used as the pump chamber pumping being carried out by external compression of the tube Occlusion of this tube at either end for appropriate periods of the pumping cycle provides valvular action and gives direction to the flow This valvular action allows of alteration of the amount ejected at each pumping cycle by changing the amount of compression of the tube at each stroke and hence the output can be varied independently of pump rate Providing compression of the tube is never complete except at the valve sites the action of such a pump is minimally traumatic to blood and allows precise regulation of both flow rate and output pattern The simplicity of assembly and adjustment together with the use of disposable tubes makes such a design practical and refinement should add further assets

An alternative to this type of pump is that known as the occlusive roller type In Europe the name Jouvelet (6) and here in the United States that of DeBakey (7) is attached to two good examples Rollers are used to occlude an elastic tube in such a manner that when these rollers are moved along the tube their action is to squeeze out blood contained in the tube No valves are ordinarily used to prevent back flow this action being provided by the sequence of operation When one roller finishes its stroke along the tube another has already begun its course along it.

The output from such a pump is pulsatile in that the change

or aeroplane, but where the fluid pumped is blood such inefficiency must be paid for in haemolysis In addition to "slipping," propellors also "cavitate" Areas of very low pressure form behind the leading edge of the rotating blades and draw from the fluid a great deal of dissolved gas Apart from the destructive forces involved this attribute is potentially dangerous in its tendency to form bubbles

It may be argued that there is no need to spin a screw within the flow—that some form of centrifuge could be used This is indeed true but in a continuous flow centrifuge there remains the problem of joining the spinning member to the delivery tubes Here an effective rotating coupling could undoubtedly be devised but this does not altogether answer the problem At some point the flow must be suddenly rotated and then delivered to a non-rotating tube At these points there is a tendency to form the sort of vortex that accompanies the emptying of a bath and such vortices have the same properties as the cavitation areas on a propeller

No stress need be made of the practical difficulties attending the construction, cleaning or sterilizing of such a pump These problems are common to all designs but probably are exaggerated here by the difficulty of allowing for a fully disposable unit

Problems of control of the output of such a pump are many Such devices do best when run at a constant speed against a constant load To arrange for accurate control against variations in resistance is necessarily complex and mitigates against successful use The only useful application of such a pump, could the many problems in design be solved, would be in maintaining recirculation within a heart-lung machine where both flow rate and back pressure can be held constant

PULSATILE FLOW PUMPS

Unlike the continuous flow pump, those of pulsatile type require some form of valve to give direction to the flow and of course produce a discontinuous pulsing output The type of pulse produced can be of infinite variety and may be of such low amplitude as to appear non-existent All the pumps in current use in heart-lung machines are of pulsatile type though the form of out-

hydraulic systems offer scant opportunity of manual intervention in the event of a power failure and imply a possibility of forcing either gas or fluid into the bloodstream in the event of a fault in the pump tubing itself

With one additional attribute any of these pumps can be made close to ideal In order to guard against the possibility of aspirating air while pumping most heart lung machines have safety devices and alarms Most depend on some form of electrical relay and some are complex This should not be necessary Suitable modifications to existing pump designs should eliminate any possibility of the pump ejecting other than fluid and should enable external controlling systems to be dispensed with The guiding factor should be the tube "stretch reflex" as in the natural heart Tubing moulded with a flat section of potentially large capacity but at rest without lumen can be substituted for that of round section and arranged to respond only to the filling pressure of blood entering it Thus the stroke volume of a pump using such a tube will automatically alter to accommodate to the flow offered to it Calibration of a reservoir directly in kilogrammes of body weight would seem a logical step with such a system and the only supervision required after filling to the indicated level would be occasional topping up to maintain it The very elegant pump used by Clarence Dennis (8) and his associates employs this principle and it seems destined to find a secure place in the future

If but a clear specification based on present knowledge of requirements can be agreed upon there can be no doubt that a technology which could master nuclear energy in a decade could produce a safe simple and effective mechanical heart

REFERENCES

1 Selkurt, E E Effect of pulse pressure and mean arterial pressure modification on renal hemodynamics and electrolyte and water excretion Circulation 4 541-551 1951

2. Ritter E R Pressure/flow relations in the kidney alleged effects of pulse pressure Am J Physiol. 168 480-489 1952.

3 Parsons R J and McMaster P D The effect of the pulse upon the formation and flow of lymph. J Exper Med. 68 353-376 1938

over from one roller to another is marked by a momentary fall in forward flow. The pressure curve shows a sustained mean pressure interrupted at intervals by a fall in pressure coincident with this changeover.

The advantages of such a pump are many and simplicity is particularly an asset. However, the action of the pump requires that the tube be occluded completely and that this occlusion be carried along the tube. This has the effect of scrubbing one wall of the lumen of the tube upon the other with attendant trauma to the blood. There is no alternative to this. To be usefully competent, occlusion is essential and the addition of valves cannot affect the action at all. This is a disadvantage which has not affected its very successful exploitation to date and it is only when a drive to further refinement is sought that it will outweigh the obvious advantages.

Similar in character to the roller pumps and sharing with them a scrubbing action is a variation known as the Sigmamotor pump. Here progressive occlusion along a tube is carried out by a series of compressing fingers. This pump has commanded a very large use, and has greatly furthered the development of the heart-lung project. Rather crude, it has at present some limitations and in action cannot escape the penalty of all wholly occlusive systems. Refinements will undoubtedly advance its claims. The output is pulsatile but of low amplitude.

Each of these three types has merits and demerits and it is proper at this stage in the evolution of the heart-lung machine to continue to explore each system. All share the useful attribute of allowing of the inexpensive disposal of all material with which blood comes in contact and have eliminated the interference to flow of internal valves. All are relatively simple in character and have no mechanically elaborate parts. The non-occlusive type offers a wider range of use, is less traumatic, and is less likely to fail from destruction of the tubing within it. On the other hand a high amplitude pulsation, if not adequately damped, may involve excessive fluctuations of flow and pressure and may become more traumatic than the low amplitude type.

Force is mechanically transmitted to the pump chamber in each of these designs—a worthwhile safety factor. Pneumatic or

hydraulic systems offer scant opportunity of manual intervention in the event of a power failure and imply a possibility of forcing either gas or fluid into the bloodstream in the event of a fault in the pump tubing itself

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6 Henry, L and Jouvelet, P Appareil à transfusion du sang Bull Acad de méd , Paris *111* 312-319, 1934

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8 Dennis, C Certain methods for artificial support of the circulation during open intracardiac surgery Surg Clin N America *36* 423-436, 1956

DISCUSSIONS ON PUMPS

DR VIKING O BJORK Stockholm All pumps give a certain degree of hemolysis There are two ways of decreasing this hemolysis First as few pumps as possible should be used We have from the beginning

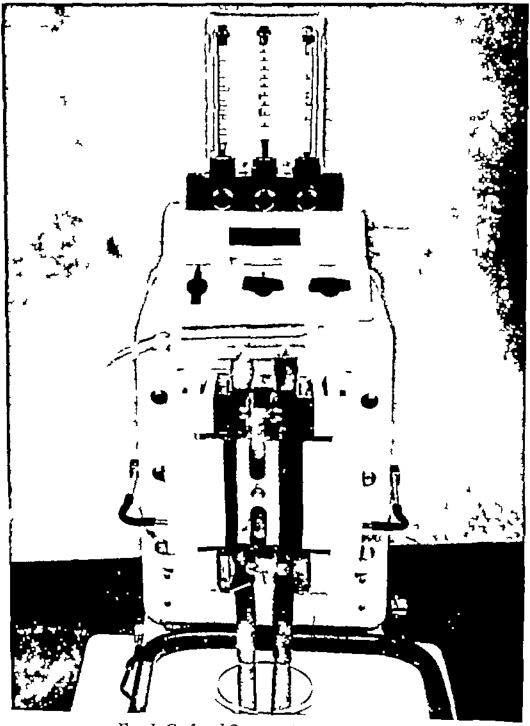


FIG. 1 Crafoord Senning Aga pump (Bjork)

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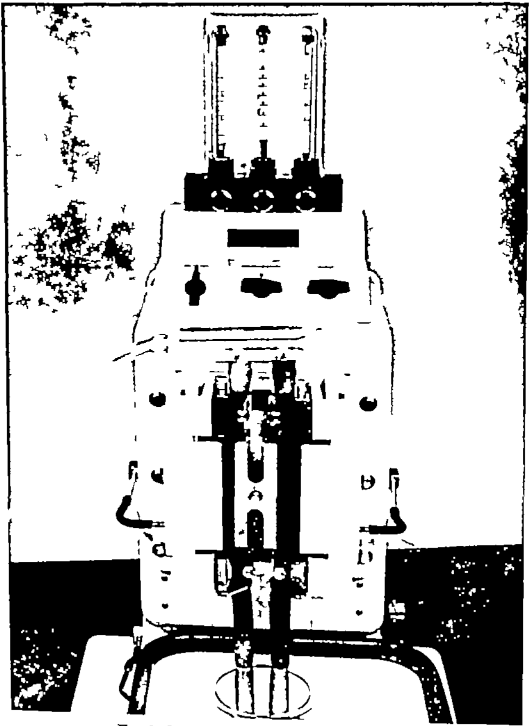


FIG 1 Crafoord Senning Aga pump (Bjork)

used a system where venous blood is drained by gravity from the vena cava through the spinning disc oxygenator Thus only one pump has to be used, the one for pumping the blood back to the arterial system

Secondly the pump should be as atraumatic as possible To move a column of blood, the tubes must be squeezed But undue trauma to the red blood corpuscles will result either with a high pulse pressure difference or with a small stroke volume In order to avoid a

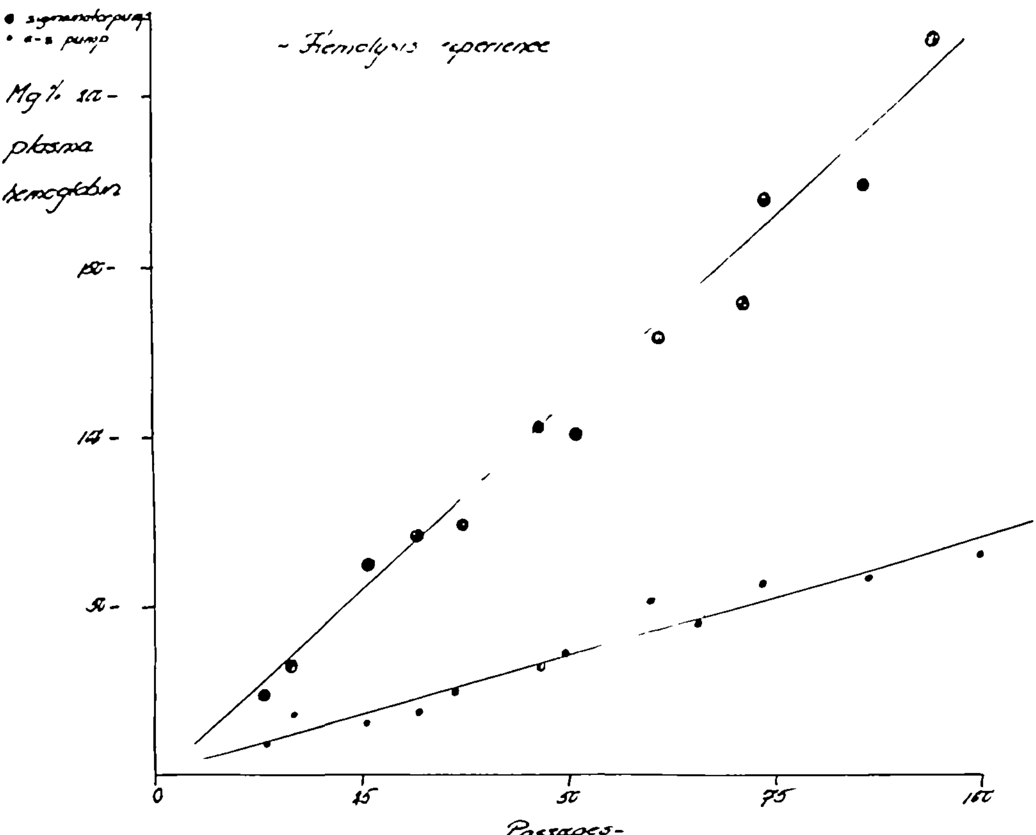


FIG 2 Hemolysis from Sigmamotor pump in upper line, lower line is that of Crafoord-Senning-Aga pump after same passages of blood through each (Bjork)

too high pulse pressure difference between systole and diastole we have from the beginning used two parallel pumps working alternately, so that when one is in systole, the other is in diastole That means that the pulse pressure difference between systole and diastole is diminished We believe this narrow pulse pressure difference will decrease hemolysis when the column of blood is forced through a narrow arterial cannula In this respect the roller pump of DeBakey type is theoretically ideal

The other factor of importance for hemolysis is the stroke volume The more often the column of blood is suddenly interrupted in a pump

with a small stroke volume the greater is the trauma to the red blood corpuscles at a higher speed Therefore a pump with as big a stroke volume as possible is theoretically ideal The Melrose pump can have a rather large stroke volume The Sigmamotor pump on the other hand has a comparatively small stroke volume resulting in a comparatively high degree of hemolysis In our laboratory Drs Anderson and Rodriguez compared the hemolysis in the Crafoord Senning Aga pump which you see in Fig 1 with the two parallel tubes being alternately squeezed with that produced by the Sigmamotor pump (See Fig 2) Under a flow rate of 2000 c c per minute circulating blood through the pumps after 100 passages through the pumps hemolysis was roughly three times more in the Sigmamotor pump The same comparison should be done with all pumps I believe the pump should maintain a constant flow of a desired magnitude

DR R L. BOWMAN Bethesda From what has been said it is apparent that blood can be pumped around by various means with a minimum of damage to the blood The hemolysis referred to may not be of much importance per se with a well perfused kidney but it does serve to indicate rough handling and should be avoided.

Further improvement in pumping systems leaves the problem of increased availability reduction in priming volume and elimination of assembly maintenance and clean up time One approach is a sterile package containing pump connecting tubes and cannulae all disposable We have made up such an assembly to evaluate this idea, and I have here Dr Selwyn McCabe s current preparation It consists of two vinyl sacs with molded valves enclosed in the outer more rigid enclosure that permits compression of these "ventricles" by injection of water into the outer space The motive power for the hydraulic pulse is provided by a remotely located actuator

The small size and smooth contours allow its placement in or near the operative site minimizing prime volume heat loss and contact of blood with foreign surfaces Currently we are using an electric motor driven variable stroke actuator and several kinds of pneumatic-hydraulic constant stroke volume systems including various self regulating features

The use of pneumatic power from a tank of compressed gas has the attractive features of simplicity and freedom from electrical power failure problems At the moment we are still using electric valves but an air valve similar to the Emerson ventilator valve is expected to replace them

Constant stroke volume variable rate systems appeal to me as a convenience in indicating flow volume We realize a similar package for the oxygenator is next but that is another problem

DR ROBERT E GROSS, Boston, Mass In discussing pumps, we would like to describe briefly a pump-oxygenator which we have constructed and found to be extraordinarily efficient, reliable, of great capacity, and also simple to operate

This unit is mobile and can be easily wheeled toward the head of

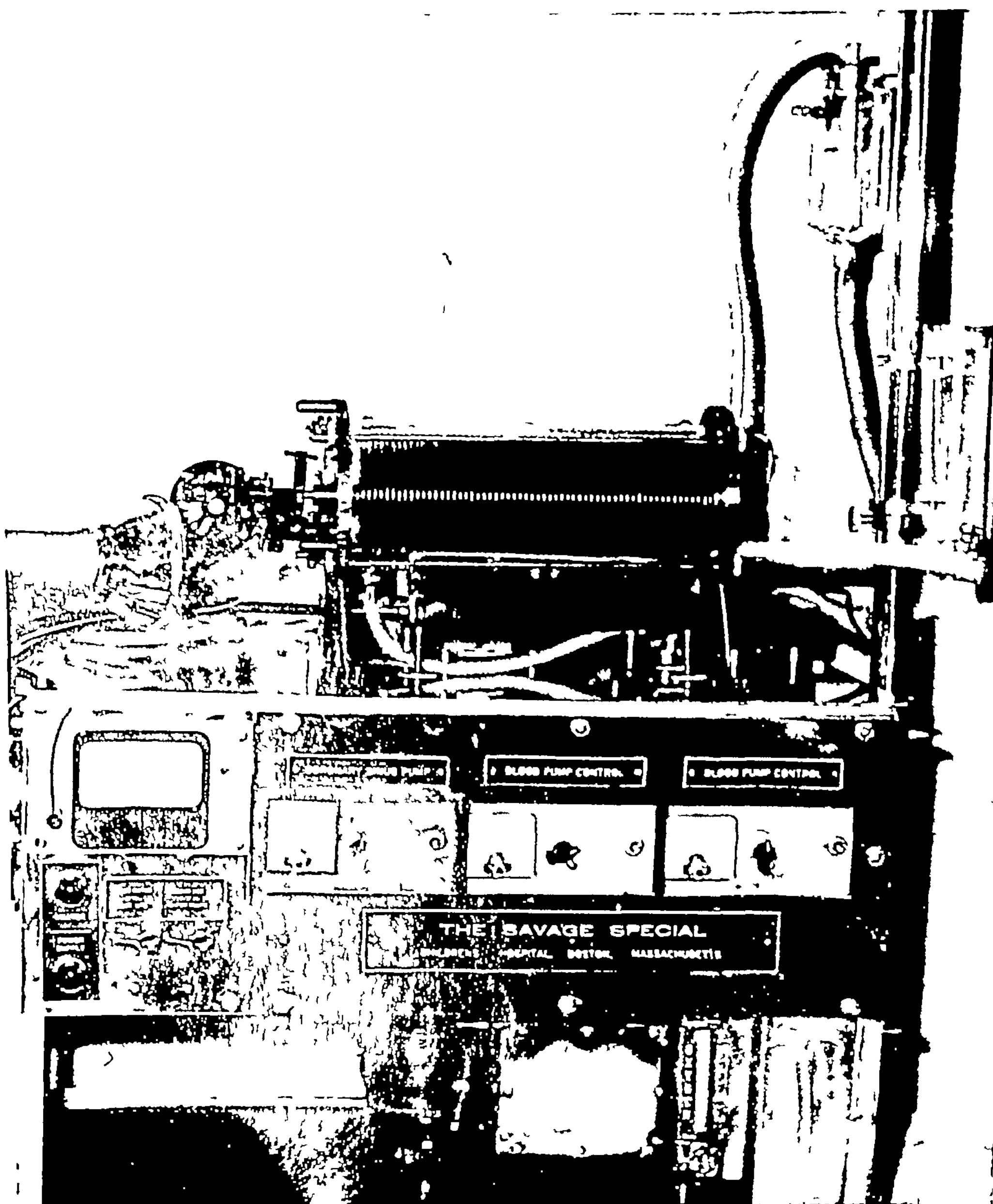


FIG 3 Pump used by Gross

the operating table From photographs we can point out some of the salient features of the machine and trace the course of blood through it, Fig 3 All caval blood runs by gravity into a collecting unit the height of which can be varied and which is generally set 8 or 10 inches below the level of the right auricle Blood from the coronary sinus or open heart is sucked away by a DeBakey type pump and is *also* delivered into this receptacle All of the blood then runs downward to the "settling chamber" which provides a smooth flow of blood through the oxygenator without bubbles or turbulence The oxygenator is a Kay-Cross rotating disc apparatus which we cannot praise too highly It has performed magnificently The only change we have made in it from the manufacturer's model is to use thinner spacers between the discs to permit mounting 25% more discs on a rotating shaft

From the bottom of the oxygenator blood is moved by a non-occlusive DeBakey type pump which we have altered slightly from the ones manufactured by the Mark Company These are nicely designed and constructed Looking down on the machine from above one can see at the back the two roller pumps one of which is used for the main pump and the other for activating the coronary sucker Fig 4 Blood

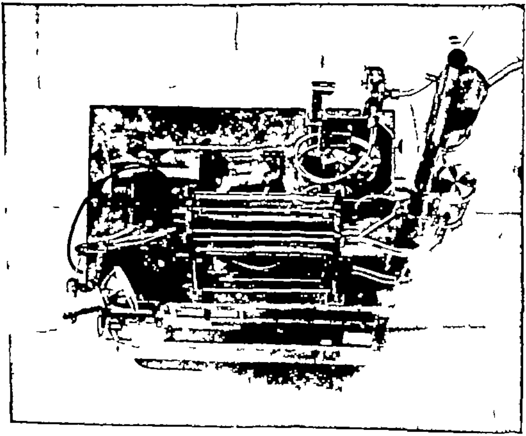


Fig 4 Pump viewed from above (Gross)

is returned to the patient by conventional cannula in a subclavian artery

Here is another view of the machine, angled from the front, showing the collector, the settling chamber and the oxygenator, Fig 5 Within

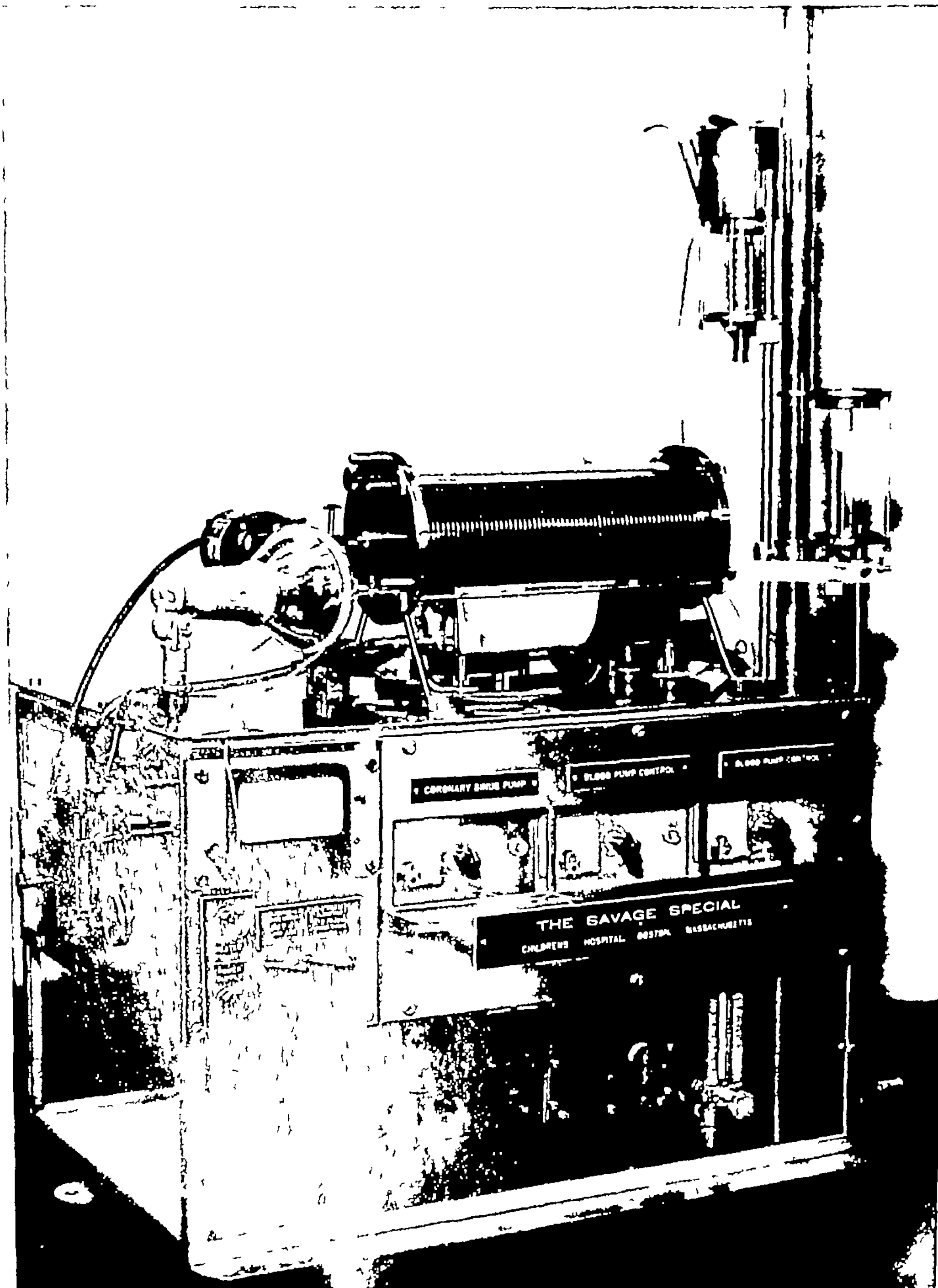


Fig 5 View showing collector, settling chamber and oxygenator (Gross)

the machine is a small water tank electrically heated and thermostatically controlled From it warm water is passed up through this metal compartment on which the belly of the oxygenator rests thus warming the circulating blood to a proper level The blood temperature electronically measured can be read at all times on the indicator at the left To the right are switches and controls for the pump motor

Great care has been taken to make the machine explosion proof All metal or glass surfaces which will be touched by blood are coated by a baked-on silicone *All* parts which will be touched by blood are sterilized by autoclaving The pumps have capacities up to 5000 c c per minute The oxygenator very comfortably ranges somewhat up above 4000 c c per minute We have perfused pups as small as 5 kilograms and have carried adult humans with ease On a test run (not connected with an animal or human) blood was recirculated through the entire machine for two hours at a speed of 3000 c c per minute Blood at the end of this run showed no essential change in platelet counts and there was an accumulation of only 13 0 mgm% of hemoglobin in the plasma. Our longest run on a human has been 63 minutes at the end of which time the plasma hemoglobin was only 21

To date 13 patients have been perfused with this apparatus *all* are alive The machine has functioned in an amazingly satisfactory and simple manner It is run by *one* person—a nurse We would not call this pump-oxygenator "*perfect*" but it is mighty close to it and we are completely pleased with it in every way

In the development and study of this apparatus I am indebted to my confreres Dr Sauvage Dr Pontius and Dr Watkins

DR. DWIGHT E HARKEN Boston, Mass In assistance through such partial venous take-off (femoral or even by cannula closer to the right atrium) arterialization and pump return to the femoral artery we are speaking of assistance without opening a body cavity

If such auxiliary take-off is only 1000 c c. of venous blood, a tremendous work reduction to the ventricles is already effected. When this venous blood is arterialized and returned, perhaps to the femoral artery or even by cannula to the lower aorta, there must be some advantage in certain pulsatile return patterns though just what this is so far as I know is yet to be determined In short, it seems likely that the returned arterialized blood should be returned during diastole when the aortic valve is closed This would probably offer less resistance to the ailing heart s systolic effort and therefore presumably less cause for myocardial work which of course is our objective

We have been working on such a pump with Dr Gants and Mr

Birtwell of the Davol Company This sturdy, versatile pump has equal adaptability for medical or surgical purposes

Fig 6 shows a bubble-oxygenator of bubble type where de-bubbling takes place in a series of concentric cylinders surrounding the central bubbling cylinders This seems about comparable to other oxygenators We use it because it is effective (as such go), it is simple, easily cleaned and it is *ours* This is not germane to this discussion The pump beside the oxygenator is shown with an oxygen tank to convey an impression of size The two rubber "ventricles" can be seen They are cylinders of cloth reinforced rubber walls The inner wall can be distended to displace blood in the transit chamber (Fig 7) The ventricles can be oper-

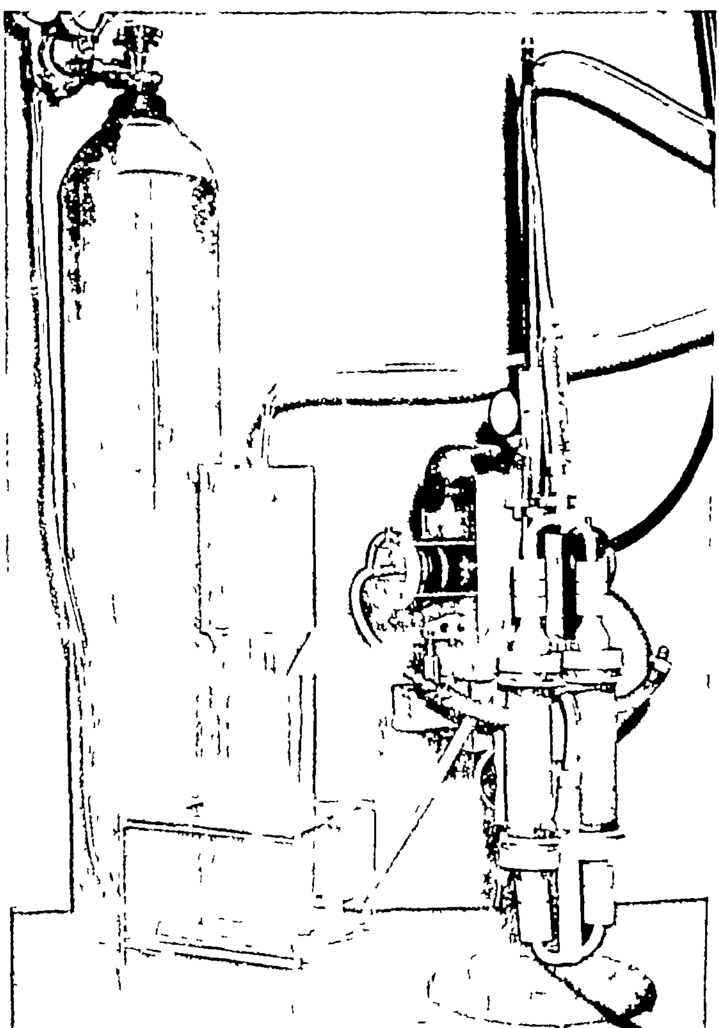


Fig 6 (Harken)

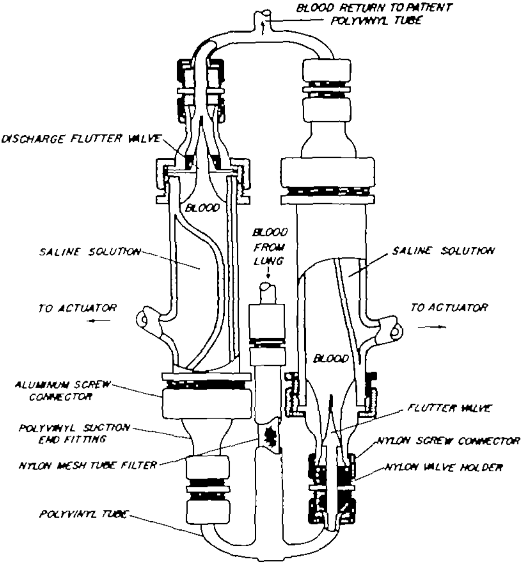


FIG 7 Diagram of circuit used by Harken

ated manually if necessary Each ventricle has a uniflow rubber inflow flutter valve at its base, an outflow flutter valve at its top (see diagram) The compressing wall can never touch the chamber wall to traumatize blood The stroke volume is changed by the amount of compressing wall displacement with saline (see diagram)

The amount of saline displacement is regulated by the stroke volume of the pistons on a single shaft (Fig 8) The screw control on the shaft alters the piston stroke and therefore the stroke volume of blood delivery This piston is impelled by compressed air (see diagram) The amount of this pressure regulates stroke speed Thus we can control pump systolic speed, volume and frequency

In the diagram you see micro-switch control which is of course automatic and for surgical by-pass use For *medical auxiliary circulation* it will probably be better to have this micro-switch mechanism replaced by a *synchronizing oscillator* so that we can have slave correlation to the QRS complex of the electrocardiogram This synchronizer is now under construction and will allow us to time the assisting pulse at any point in diastole or even fibrillate with a heart in auricular fibrillation for complementary or paradoxical volumetric stroke assistance The second diagram clarifies this pump set-up Again (Fig 9), we can take a closer look at the activator aspect of the pump Dr

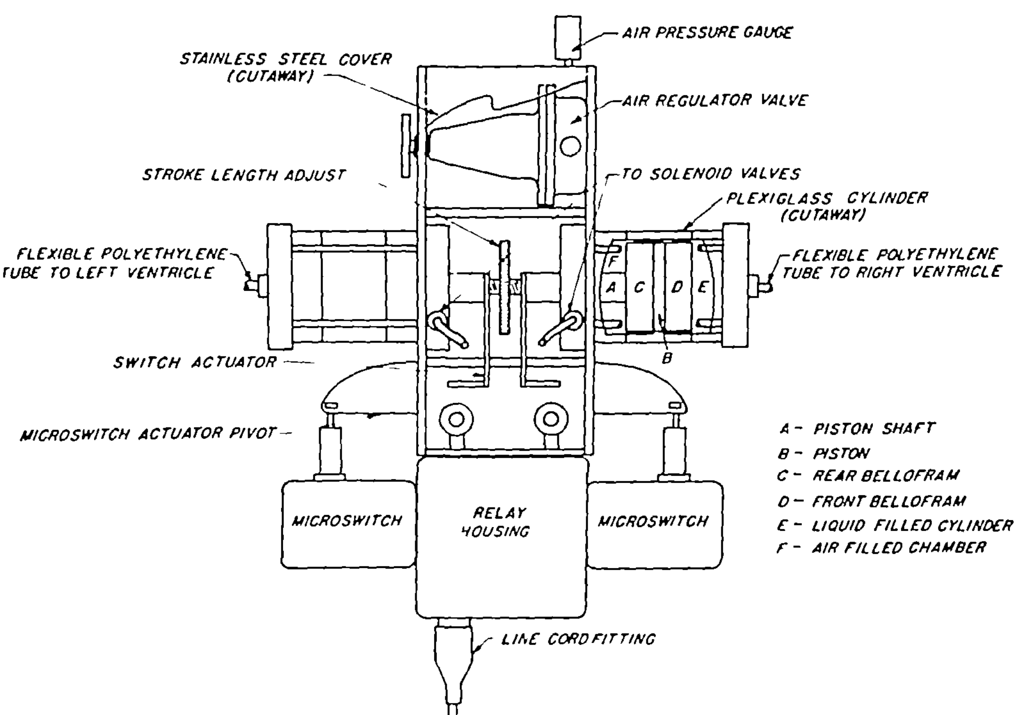


FIG 8 Diagram of pump (Harken)

Gants and Mr Birtwell of the Davol Company have built

In closing I should like again to stress the vastly important medical area awaiting the right pump-oxygenator The significance of venesection involved may be a very major part of its total value We have today presented a pump with a great flow of variability and as little traumatic effect on blood as any of the pumps we have tested In addition it has versatility through stroke volume frequency speed and timing

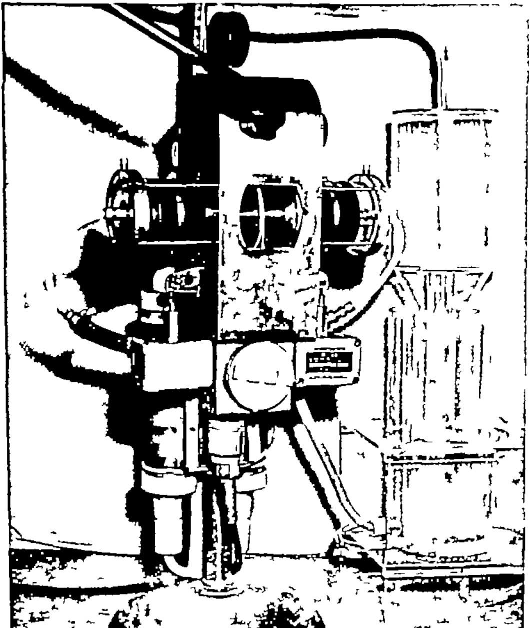


Fig 9 Photo of pump (Harken)

ated manually if necessary Each ventricle has a uniflow rubber inflow flutter valve at its base, an outflow flutter valve at its top (see diagram) The compressing wall can never touch the chamber wall to traumatize blood The stroke volume is changed by the amount of compressing wall displacement with saline (see diagram)

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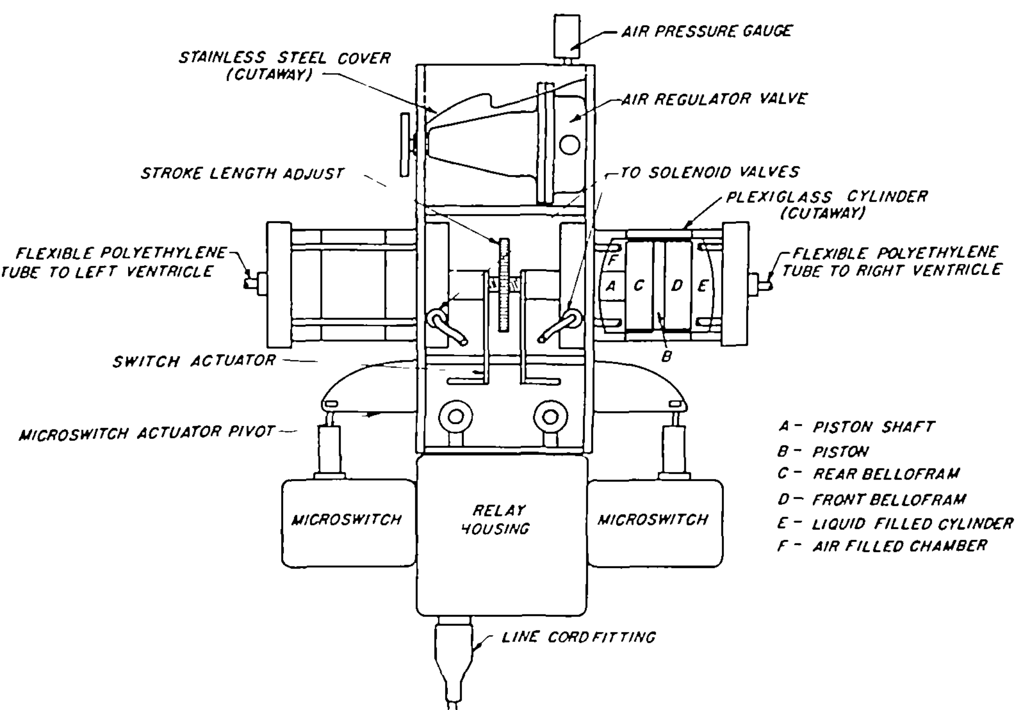


FIG 8 Diagram of pump (Harken)

PRESSURE CHANGES IN THE CHAMBER OF THE PUMP AND ACTION OF THE VALVES

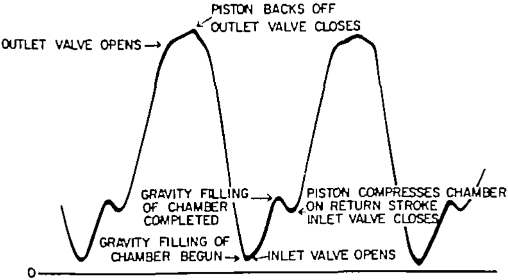


FIG 11 The time for a complete cycle is 0 8 seconds Time intervals can be taken by direct measurement from the curve The maximum pressure is 160 mg Hg (Poth)

DR WILLIAM H SEWELL, Atlanta I think it is pretty definitely apparent from what we heard today and what is going on in the country as a whole that there are a number of pumps that are working satis factorily when things are going well and the subject is not in shock and the venous pressure is at a satisfactory level. However when you are not getting as much blood back from the cavae as you would like there are some minor differences in the design of the pump which may be of importance A pump with passive internal valves has features of some value here When a passive valve closes there is bound to be a puff of blood back into the venous tubing as the valve is going down Dr W W L. Glenn and I have found in New Haven that this backflow is adequate to push the cavae away from the holes in the cannulae when the vessel has collapsed This means the pump is practically self regula tory During each diastole of the pump the cavae may be sucked against the cannulae but are released for the next systole With an air activated system, it does not matter whether you are sucking too hard over a wide range because of this principle

DR EDGAR J POTH, Galveston, Texas I wish to describe briefly a pump we have developed It is one of non-occlusive-pulsating flow The pulsations can be modified by a modulator or completely eliminated if desired The valve in this pump is illustrated in Fig 10 The pumping action is dependent upon a piston which merely compresses the pump chamber The volume of this pump is adjustable to a maximum of 6 liters of blood per minute

The vanes of these valves are supported in the center There is a small stainless steel support across the orifice This valve is tygon with an inner support of stainless steel The chamber consists of tygon and has no restoratory power It can only fill by gravity The slide shows the inlet and outlet valves

Figure 11 shows the form of pressure curve inside the chamber The cycle can be followed readily from this pressure curve When 100 liters of blood is pumped through a four-foot length of ¼-inch tubing in 30 minutes, the plasma hemoglobin increases 0 67 mgm % Should the power fail, you can operate the pump by hand by simply squeezing the chamber

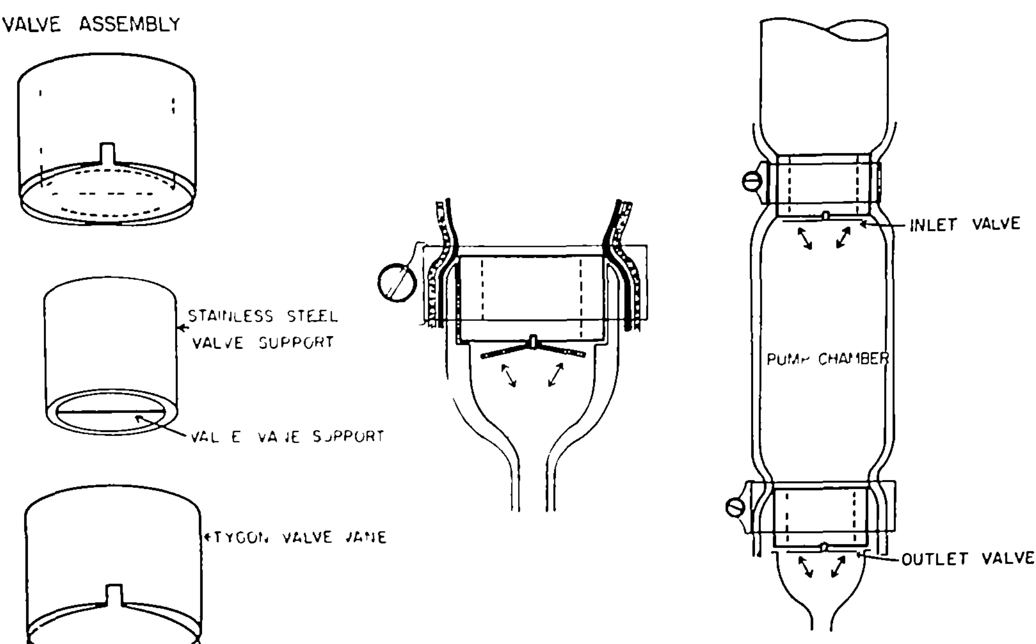


FIG 10 The valves are the most important portion of this pump They are competent, rapid in action and cause no trauma Excepting for the valve housings, which are made of stainless steel, the entire inner surface is of tygon (S-22-1) and is disposable (Poth)

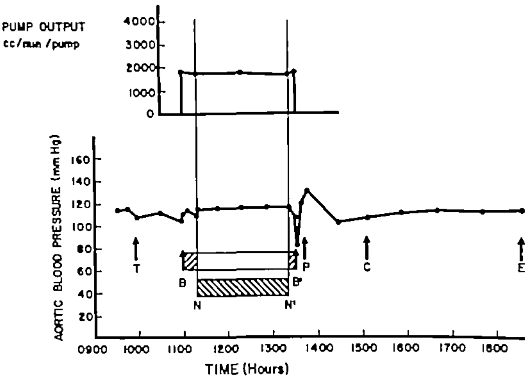


FIG 13 Shows balance of "take up" and "yield up" for three hours of use (Wesolowski)

monary artery was occluded by ligature Blood was oxygenated with homologous lungs In addition the bronchial venous return was aspi rated into the pump system via a cannula inserted into the left atrium this was necessary to attain a strictly non pulsatile flow by preventing pulsatile ejection of the small return to the left heart. Blood was then pumped into an elevated open reservoir from which the entire systemic circulation was perfused by gravity through a cannula in the left sub-clavian artery On the right of this slide the middle blood pressure trac ing demonstrates the strictly non pulsatile character of the perfusion. Figure 13 demonstrates that during the average 2 hour period of non pulsatile perfusion the blood pressure remained remarkably constant at about 115 mm Hg while the pump output similarly remained constant at 125 c c /kg /minute During non pulsatile perfusion maintained for as long as six hours the blood balance at the end of perfusion was essentially zero and the animal exhibited no "take up" or "yielding up" of blood PSP studies of renal excretion demands for anesthesia and vas cular reactivity to vasoconstrictor and vasodilator drugs remained normal during the non-pulsatile perfusions when compared to animals perfused with pulsatile flows

I think, however, that this type of pump is hard to keep stable with the caval pressure at any level above complete emptying

Therefore, the pump we are using in Atlanta is the Sigmamotor We handle the collapsing problem in this manner The venous pressure is kept a little above normal by sucking excess blood into the oxygenator, with the arterial pump left constant When one of the cavae should collapse, increased suction is forced on the other one which is apt to collapse also Particularly helpful is a manometer connected to the venous reservoir The usual suction is about 25 mm Hg If the vena cava collapses, the suction here rises rapidly to about 200 mm Hg and we can tell from that that it has collapsed and turn down the venous pump after temporarily pinching the tube to release the vein We favor constant venous suction achieved by air in a closed venous reservoir We do not use gravity drainage to avoid the necessity of adjusting both the *syphon suction and also the venous pump, and to avoid any constriction* used to adjust the former

SIGMUND A WESOLOWSKI, Brooklyn, N Y I should like to compliment Dr Bahnson and Dr Melrose on their fine presentations and to show two slides that summarize results demonstrating that for periods of time of at least six hours, a strictly non-pulsatile flow is as efficient as a pulsatile flow during complete by-pass of the heart and lungs Figure 12 shows the schematic circuit for by-pass of the heart and lungs using pumps and isolated homologous lungs Blood was quantitatively aspirated out of the right atrium into the pump apparatus, the main pul-

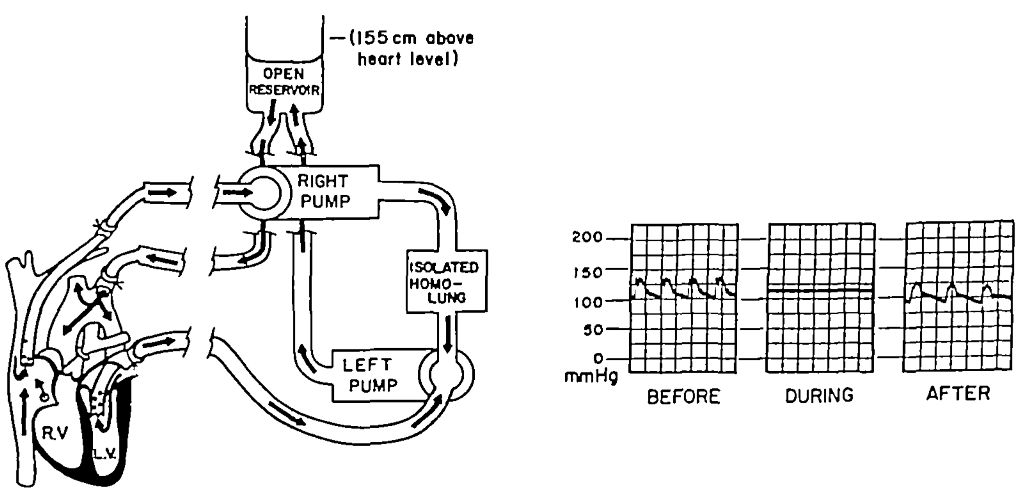
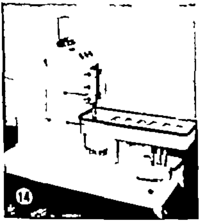
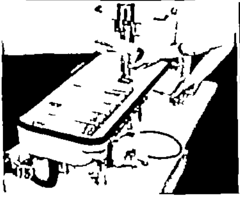


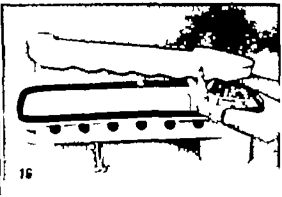
FIG 12 Schematic circuit for by-pass, using pumps and isolated homologous lungs (Wesolowski)

vessel During rotation the cylinders become coated with blood which is thus spread out in a thin layer and offers a considerable contact surface to the atmosphere in the oxygenator The gases are supplied in suitable proportions to the basin via flow meters The basin with its collecting vessel is fixed in a metallic trough The oxygenated blood collects in the collecting vessel and is pumped from it by the pumping device back to the patient s arterial system



Figs 14 15 and 16 Functioning units of pump used by Senning





In patients weighing more than 20 kg two basins containing 12 rotating cylinders are used For heavier patients a pre-oxygenator is added In this 50-100 ml. of oxygen is allowed to pass a filter with a porosity of 3-4 microns directly into the blood before its passage through the machine When one basin is used the machine holds 1 6 liters of blood, 2.1 liters being required when two basins with 12 cylinders are used and 2.4 liters with pre-oxygenator In addition the machine has a reservoir containing one liter of blood for compensation of any blood loss

The hemolysis during the operations has been 15-55 mg% except in one patient When fresh human blood is recirculated in the pump and the tube system without cannulae in vitro it results in hemolysis

One further point concerning pump machines is worth repeating and stressing This is the problem of safety of the apparatus Safety is essentially a matter of control devices Certain apparati, including certain continental ones demonstrated at the recent artificial heart-lung symposium in Turino, Italy, are beautifully resplendent with all sorts of control devices, both mechanical and electronic It appears self-evident, however, that the safest machine will be the one which incorporates into it by the nature of its design the maximum control and requires therefore, a minimum number of compensatory safety devices In other words, the ideal machine, like the ideal wife, is that one which necessitates the minimum of control

DR MICHAEL DeBAKEY, Houston, Texas I would like to clarify some possible errors in statements about our rotary pump First, there is the problem of whether or not it is necessary to have complete or incomplete occlusion of the tubing In our early work it was apparent that total occlusion was not necessary and was possibly harmful Alteration in the rotary rate of the roller arms was the best method of controlling or regulating the rate of flow Moreover, in studies concerned with hemolysis produced by the rotary pump we found it was better not to have complete occlusion but partial occlusion Apparently no difference in degree of hemolysis was noted at varying degrees of partial occlusion of the tubing The degree of negative pressure created by the pump appeared to be more significant in producing hemolysis than the degree of positive pressure Second, in studying factors controlling rate of flow through the pump, we found that the resistance to both inflow and outflow were the most significant particularly when the tube was partially occluded Thus, no matter how fast the pump rotated the outflow was controlled by resistance The same was true for the inflow We concluded on the basis of these and other experiments that the roller type pump was the most satisfactory mechanism for propelling blood in a closed system

DR AKE SENNING Stockholm, Sweden The machine we use has been developed at Sabbatsbergs Hospital It consists of an oxygenator and a pumping device combined with a regulating unit, Figures 14, 15 and 16 The blood is withdrawn from the patient's venous system and conveyed by gravity into the oxygenator via a flow meter The oxygenator consists of a basin containing six disposable rotating cylinders of perforated plastic foil By rotation of the cylinders the inflowing blood is conveyed to the outlet end of the basin and is collected in a

amounting to 0.5 mg% per each passage Corresponding tests with the two basins and 12 cylinders give a little less than 1 mg of free hemo globin each time

In our oxygenator laboratory we have been using bubble oxygenators of different types DeWall s etc. They are simpler and have several advantages but in my hands bubble oxygenators gave higher hemolysis and protein changes I cannot say that there is a better survival rate with the one or the other and it seems up till now more important what team is driving the machine than what type of machine they use What has to be made now is a more thoughtful study of blood changes biochemical changes enzymatic changes and cell permeability That perhaps can give us an idea of differences not now evident

DR. I H RYGG Copenhagen We have for the last one and a half years used an eccentric roller pump of the occlusive type and we are very satisfied with its function

Figure 17 shows you the heart lung machine with the eccentric roller pump at the right. For several reasons we wanted to have this type of pump Figure 18 shows you a diagram of the principle used in this pump-oxygenator Blood from the caval veins and from the vacuum chamber used for aspiration of the cardiac blood during operation is led to the oxygenator by gravity Thus pumps in the inflow lines of the

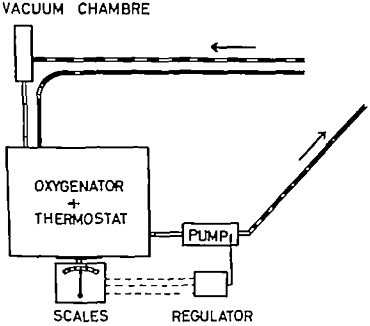


FIG 18 Diagram of circuit of pump oxygenator used by Rygg

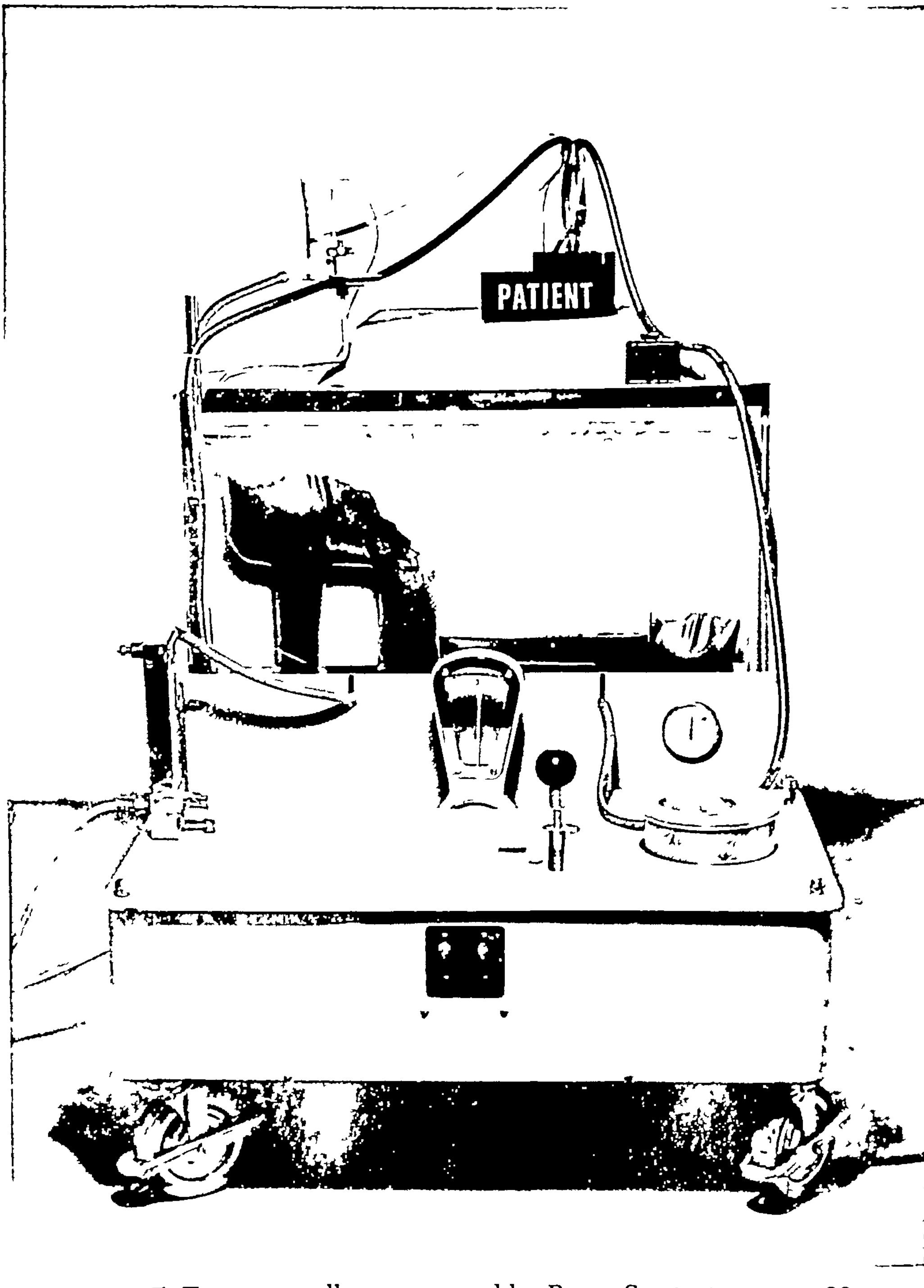


FIG 17 Eccentric roller pump used by Rygg See text on page 39

THE HELIX RESERVOIR BUBBLE OXYGENATOR AND ITS CLINICAL APPLICATION

By

RICHARD A. DEWALL, M.D.,* HERBERT E. WARDEN, M.D., *and* C. WALTON LILLEHEI, M.D.

THE HELIX reservoir bubble oxygenator has had repeated clinical application as an aid to open cardiac surgery since May of 1955 at the University of Minnesota Hospitals. A number of other groups as well, have found a bubble oxygenator and perfusion system similar to that described in this paper to be of value.

The successful outcome of visual intracardiac surgery is dependent upon the design of the perfusion apparatus and its method of application, the use of proper surgical techniques, and appropriate postoperative management of the patient. Many aspects of perfusions pertinent to the latter two categories mentioned are common to all systems of extracorporeal circulation.

THE HELIX RESERVOIR BUBBLE OXYGENATOR

The helix reservoir bubble oxygenator† (Figure 19) consists of three major components: the blood-oxygen mixing tube, the de-

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*Research Fellow, American Heart Association.

This work was supported by research grants from:

1. American Heart Association
2. Minnesota Heart Association
3. Graduate School, University of Minnesota
4. Life Insurance Medical Research Fund
5. National Heart Institute (H-830)

† Manufactured by Phelan Manufacturing Co., 2029 Washington Ave., Minneapolis, Minn.

machine are avoided From the oxygenator—that is a plastic bag one—the blood is returned to the patient by means of a pump which is the only one needed in this system By using an occlusive eccentric roller pump for this, we have at the same time a very accurate flowmeter

The oxygenator is suspended in a thermostat case and placed on a pair of scales to secure a constant blood volume in the oxygenator system The weight of the oxygenator is kept constant by adjusting the pump to keep the scale indicator permanently at zero This adjustment can either be done manually or by means of an electronic device The scales have proved to be a great advantage and have made it possible in a simple way to keep the extracorporeal blood volume within variations of 10 grams

to a flow of gas up to twelve liters per minute. This maximum quantity is considerably more than has been needed in clinical usage. The pressure in the gas line during the perfusion will be elevated also by an amount equal to the hydrostatic pressure of blood which the column of gas supports in the mixing tube. The blood-oxygen mixing tube empties from its top into a debubbling chamber. This chamber is designed to separate the excess oxygen and carbon dioxide from the arterialized blood. A double barrel mixing tube and debubbler is used for perfusions over 2500 cc/minute (Inset, Figure 19). This provides the larger debubbling surface necessary for these higher perfusion rates. A spare sterile debubbling chamber is always available that can be used to replace one in operation without interruption of the perfusion should it become ineffective during a prolonged bypass.

The blood flows by gravity through the debubbling chamber and empties into the helical reservoir where effective removal of any free gas remaining in the blood is achieved. The helical reservoir performs this function by taking advantage of physical forces which are synergistic. Free gas remaining in the blood gives it a lesser density than normal blood and consequently this less dense blood is forced upward by hydrostatic pressure. This lighter blood containing free gas therefore laminates on the upper layer within this tube. As the flow of blood is down the inclined plane of the helix, the heavier gas free blood descends by gravity beneath the lighter gas-containing blood, forcing it continuously upward. This lamination of the flow is present as long as blood of the two densities is present; however, after a short transit down the tube the lighter gas containing blood coalesces, rises upwards and oxygenated blood, free of the excess gas, flows to the bottom of the helical coil where it leaves through the arterial filters.

All of the plastic components of the helix reservoir oxygenator which are in contact with the blood are made of a pure polyvinyl plastic hose,* sterilized in the steam autoclave before use and are discarded after one application as their cost is less than the expense or potential dangers to the patient of attempting to clean and reuse them.

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* Mayon Plastics, 415 17th Avenue North, Hopkins, Minnesota.

bubbling chamber, and the helical reservoir, in addition other units are the arterial filter, the vena caval drainage reservoir (Figure 20) and the cardiotomy return system (Figure 21) The size of the oxygenator is adapted to the size of the patient and the desired perfusion rate (Table I) The blood-oxygen mixing tube is a vertical column in which the venous blood is filmed upon the surface

TABLE I

DIMENSIONS FOR HELIX RESERVOIR BUBBLE OXYGENATOR

Perfusion Rate	*Internal Diameter (Inches) and Length (cm)*		
	Mixing Tube	*Debubbler*	*Helix*
to 1000 cc /min	$1\frac{1}{2}''$ I D 65 cm	$2\frac{1}{2}''$ I D † 55 cm	1″ I D 350 cm
1000 cc to 2000 cc /min	80 cm	55 cm	450 cm
2000 cc to 2500 cc /min	95 cm	55 cm	550 cm
*2500 cc to 5000 cc /min	2 each 65 cm	2 each 55 cm	650 cm

* For these flow rates a double system is used as illustrated in Figure 19, inset

† This hose is also used for the vena caval gravity drainage reservoir and the cardiotomy return reservoir The later two chambers are made thirty centimeters in length (Figures 20, 21)

of large bubbles of oxygen This mixture gently rises in the mixing tube due to the venous blood entering and the flow of oxygen passing up the tube At the base of the mixing tube is placed a nylon plastic cylinder closed at the top by a nylon plate This plate has a central perforation large enough to accommodate the conduit carrying venous blood from the patient to the oxygenator This hole is surrounded by twelve dozen perforations approximately the size of a No 23 hypodermic needle bore Oxygen is directed into the base of the mixing tube through these perforations A properly designed oxygen dispersion plate should present a minimal resistance to the inflow of oxygen If this is not the case and oxygen is introduced under unusual force, the energy generated as measured by the pressure in the line transmitting oxygen to the system will be imparted to the blood via the gas jets causing unnecessary hemolysis The oxygen dispersion plate as described above presents only a few millimeters mercury pressure resistance

The Caval Drainage System

A gravity drainage system of the vena cavae is preferred to direct pumping as the former aids in preventing abnormal pressure rises developing in the patient's venous system. Figure 20 illustrates the system used. The lower portion of this well does not need to be more than twenty inches below the level of the

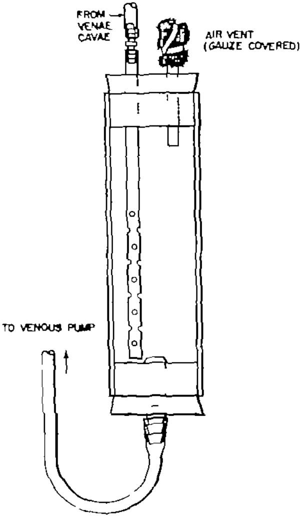


FIG. 20. The Vena Cavae Gravity Drainage System. The main body of the chamber is made of the same flexible polyvinyl hose used for the debubbler chamber. Its internal diameter is 2.5 inches and it is twelve inches in length. This vessel is placed close to the operating table and at the start of the perfusion its base is about twenty inches below the patient's cavae. After the perfusion is started it is elevated until an optimum return from the cavae is obtained, which is often about twelve inches below the level of the cavae or right atrium. (De Wall)

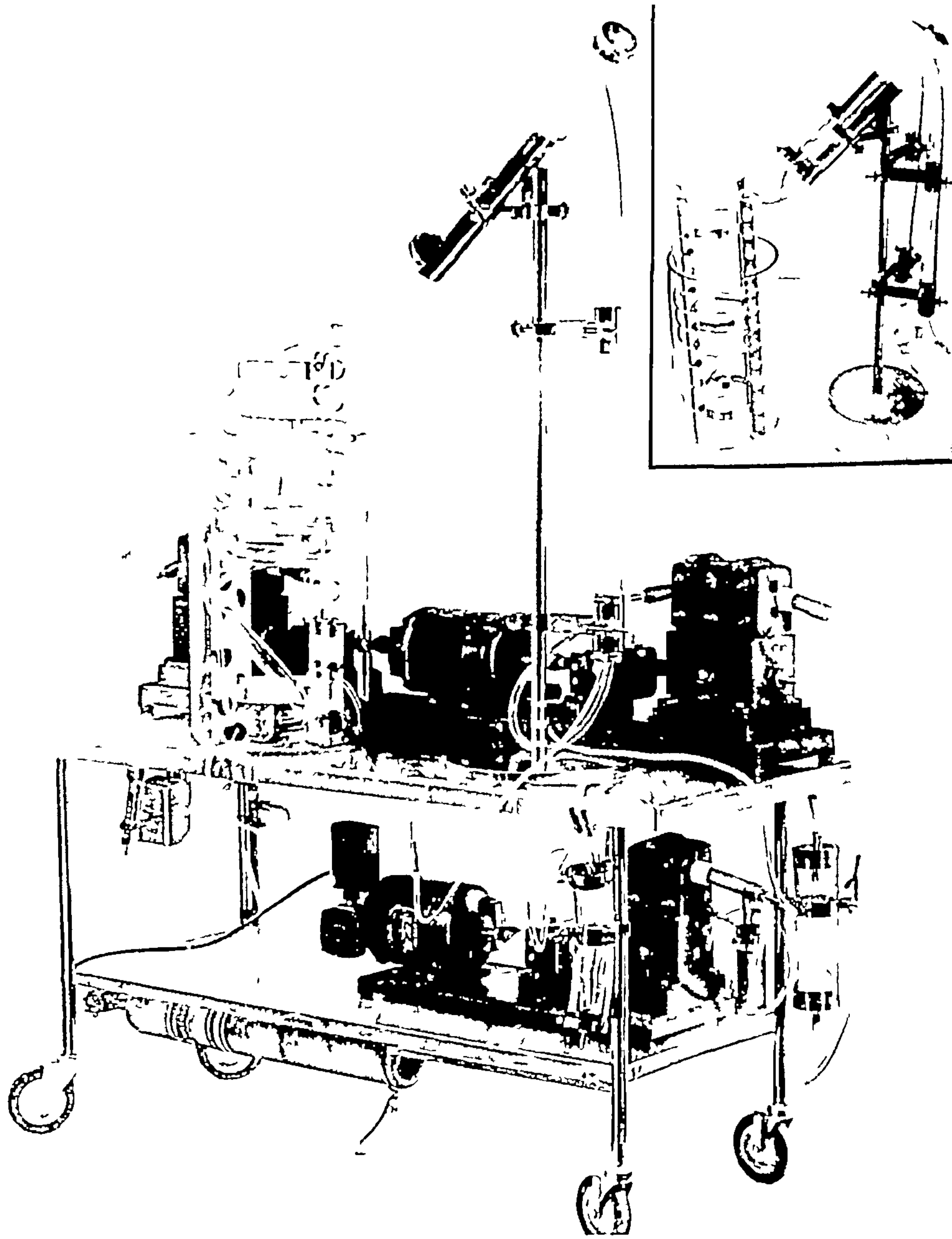


Fig 19 The Helix Reservoir Bubble Oxygenator All of the plastic components are made of a pure flexible polyvinyl plastic tubing which are autoclaved before usage After one application the tubing is discarded A water bath maintains the circulating extracorporeal blood at body temperature The pumps are the Sigmamotor type (see text) Note the cardiotomy return and gravity caval drainage chambers, respectively, attached to the table in lower foreground (Inset) For perfusions over 2500 cc minute, a double mixing tube and debubbler are used with the single helix reservoir (De Wall)

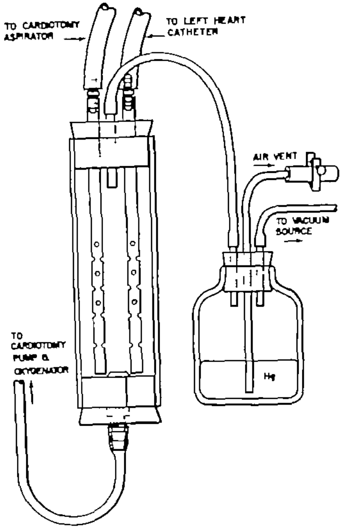


FIG 21 The Cardiotomy Return System This vessel is also made of a 2 5 inch I D polyvinyl plastic tube twelve inches in length. This chamber is equipped with two inlets one for the direct aspiration from the patient s open heart The other is a reserve tube clamped when not in use but used when a large loss from the open heart is expected such as in patients with mitral disease and some degree of aortic regurgitation A considerable blood loss also may be anticipated in older cyanotic patients due to their large bronchial collateral. In cases such as these the second inlet to the cardiotomy return chamber can be attached to a catheter which is placed into the right or left atrium depending upon the indications It also can be used to catheterize an anomalous left superior vena cava when encountered. The mercury trap bottle can be any suitable container The metal adaptors are one-quarter inch internal diameter The air vent controls the suction at about twenty millimeters of mercury Should the occasion arise to remove a large quantity of blood in a hurry the air vent can be closed by occluding the plastic adaptor on the end of the tube After the need for increased suction has passed this clamp can be released

patient s cavae After the start of the perfusion this chamber may be adjusted to a suitable level dependent upon the particular patient s venous pressure, blood volume, and the flow rate being used This level is often found to be about twelve inches below the level of the cavae If the reservoir is placed too low, the siphoning forces of the column of blood may become excessive and tend to occlude the cavae against the catheters

The Cardiotomy Return System

In clinical operations the need for returning to the extracorporeal system the blood from the cardiotomy is without question Figure 21 shows the method used A three-eighths inch internal diameter polyvinyl hose is used to conduct the blood from the aspirator to the collection chamber This hose size will return a greater quantity of blood with less vacuum than a smaller hose, but it is not too large for convenient manipulation The aspiration vacuum is set for about twenty millimeters of mercury but can be altered as the indications arise The lowest aspiration pressure that is effective is desirable, but hemolysis does not come as much from a high suction force *per se* as from the turbulent mixing of air with the blood

If the occasion arises to remove rapidly a large quantity of blood, as from the heart of a patient with mitral disease and some aortic valve incompetence, some patients with aortic stenosis, or in patients with cyanotic heart disease and a well developed bronchial collateral, the high vacuum source can be used without a proportionate increase in trauma to the blood as minimal amounts of air are mixed with the aspirated blood in such situations When the need for the removal of such large quantities of blood passes, the suction in the cardiotomy collection vessel can be returned to the desired level by release of the clamp on the air vent hose The cardiotomy aspiration chamber is placed as close to the floor as practical as this increases the siphoning effect on the aspirator tip without need for increasing the vacuum source To reduce the resistance in the aspiration tube itself, it should be as short as practical usage permits The aspirator should also be held as horizontal as possible, as each centimeter of vertical elevation of the handle increases the vacuum necessary to move the column of blood

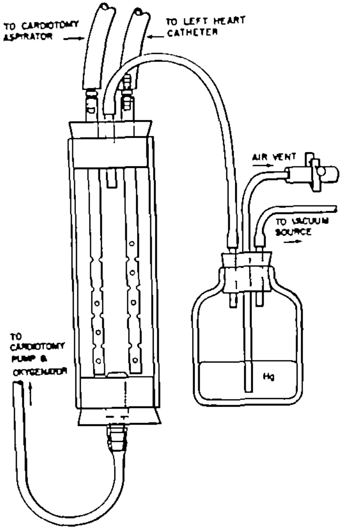


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A second connection is made available in the cardiotomy return chamber which can be connected to a second aspiration tip or catheter This can be used to catheterize an anomalous left superior vena cava, or if a large blood loss is anticipated as with patients such as described above the catheter may be placed into either atrium depending upon the indications

Oxygen Supply to the Oxygenator

Various respiratory gas mixtures have been used in the helix reservoir oxygenator, however none has had demonstrable advantages over the use of 100% oxygen We have found no evidence of "oxygen toxicity" under the conditions in which it is used in this apparatus The oxygen input to the mixing tube is three to five times the blood input During all perfusions repeated determinations of oxygen content and oxygen capacities have been made on the oxygenated blood These values are routinely checked after the perfusion The arterial blood leaving the oxygenator is maintained at 95%-98% saturation

Connectors and Filters

Some of the hemodynamics that are concerned with connectors and filters have previously been described [1] Suffice it to say that any dead space at connections must be avoided as such a defect may form a potential area for fibrin and platelet clot formation due to eddy currents at these sites We have designed *stainless steel* connectors and adapters*, smoothly polished internally and without abrupt shoulders or other obstructions, which obviate much of the potential turbulence at these sites

At the present time we are using standard infusion set filters † These filter cartridges are fitted into a specially designed methacrylate chamber which holds four filter units For perfusions less than 2000 cc /minute one chamber containing four filters is used For perfusions over 2000 cc /minute two chambers containing eight filter cartridges are used Each filter cartridge has a filtration area of 50 square cm

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* Made by Phelan Manufacturing Company, 2029 Washington Avenue So, Minneapolis, Minn

† Baxter Laboratories, Morton Grove, Illinois, Filter #CLFIB

We prefer an arterial filter which is rigid A supple sock like filter system will tend to vibrate or flap within the blood stream due to the pulsatile forces of the pump This oscillation may damage the blood and cause deposition of fibrin which may embolize beyond the filter mechanism Obviously a poorly designed arterial filter can cause more difficulty than no filter at all

Connecting Hoses

A one-quarter inch internal diameter polyvinyl tube is used to connect the patient to the oxygenator for perfusions up to 1500 cc /minute Above 2000 cc /minute the resistance in this size tubing becomes significant which in turn is reflected in a reduced efficiency of the pumps Therefore three-eighths inch internal diameter plastic tubing is used for all perfusions over 1500 cc /minute

Preparation and Sterilization of Plastic Tubing

The new polyvinyl tubes are cut to the desired lengths and washed with a laboratory detergent * After thorough rinsing in water and coating the indicated areas with the antifoam silicone the open ends of the tubes are wrapped with gauze which is held in place by special self sticking autoclave tape Each hose is then wrapped in a double thickness canvas The wrapped hoses are then placed into an autoclave taking care that one hose does not overlie another as this will cause them to become indented when heated The autoclave is then set for 250° F and twenty pounds pressure for one half hour The hoses are then dried by setting the autoclave to "steam exhaust" and dried under a mild vacuum at 150° F for one hour to three hours depending upon the thickness of the sterilizing canvases This drying is an important step and if omitted the plastic tubing will be opaque rather than clear and transparent Many units can be made up at a single time and stored in the operating suite until needed Just prior to the operation the various hose units are assembled taking care not to contaminate any of the parts which will be exposed to the blood.

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* Alconox, Alconox Inc. Jersey City 4, New Jersey

Siliconing the Debubbler and Cardiotomy Return Vessel

Dow Corning Antifoam A* is used to coat the inside of the debubbling tube, the first twenty centimeters of the helix. The caval reservoir and cardiotomy† return chambers do not require antifoam treatment. A gauze sponge soaked with the antifoam emulsion is used to place a layer as thin as possible of the antifoam in the above mentioned units prior to autoclaving. If any excess has pooled in these vessels after autoclaving, it is removed by allowing it to drain out of the tubing before assembly. A very thin coating of antifoam will perform its function better than a thick coat as this substance is active in a concentration of 1 part in 10,000,000. If a great excess of antifoam is applied to the system, it can be swept into the arterial tree as emboli. The debubbling surface in the debubbling tube is increased for larger flows by the placement of a small coil of plastic tubing also thinly coated by wiping with the antifoam substance into the tube.

Priming the Helical Reservoir Bubble Oxygenator

The oxygenator reservoir is primed to contain a quantity of blood sufficient to provide a one-minute circuit time through the oxygenator. The apparatus is therefore tailored to the size of the patient and the expected perfusion rate. The one-minute circuit time provides an adequate time interval for complete control of the patient's blood volume and the perfusion during any unforeseen temporary imbalance between outflow and inflow that may arise. For example, should there suddenly develop a diminution in venous return because of some unexpected blood loss, the team has up to one minute to adjust for the difficulty without the necessity of decreasing the arterial perfusion to the patient.

A constant temperature water bath is kept available in the operated suite, and the heparinized blood bottles are placed into this bath several hours before the surgery to be sure that the blood has attained body temperature before it is used. The temperature of this bath is set at 41° C. Those bottles selected to prime the oxygenator are each matched with all others. They are

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* Dow Corning Corporation, Midland, Michigan

† In patients where an unusually large blood loss may be anticipated we coat the cardiotomy reservoir with a thin film of Antifoam A.

placed in the venous reservoir of the oxygenator, put through the blood oxygen mixing column for arterialization, and subsequently fill the helix. The oxygen flow into the mixing column is adjusted so that it is barely adequate to push the blood through the mixing column. This prevents the oxygen tension from reaching unusually high levels during priming. The priming blood should be as warm as or slightly warmer than the water bath (41° C) that surrounds the helix reservoir. If the priming blood is colder than the helix bath, the dissolved oxygen will come out of solution as the priming blood is warmed within the helix reservoir water bath. Many minute bubbles will then be deposited upon the walls of the helix coil. If such a circumstance does occur, it is better to wait a few minutes until the temperature of the blood in the helix coil has equilibrated with that of the bath and until all the excess oxygen in solution has been removed from solution to the walls of the tube. The perfusion can then be started. These minute bubbles will not move out of the helix as bubbles but will be absorbed by the blood which will subsequently pass through the helix reservoir.

Pump Calibration and Perfusion Rates

The pump used in all of the clinical cases has been the Sigmamotor pump* which has proven to be efficient and dependable in all these perfusions. As the weight of each patient is known, an approximate perfusion rate is selected for him dependent upon his size and diagnosis. The arterial pump is then set by means of a stopwatch used to measure the rate of pumping sterile dextrose into a graduate. The venous pump is set up approximately at the same level but is altered during the perfusion dependent upon the venous drainage and the cardiotomy return. The perfusion rates are varied from fifty to one hundred cc./kg. body weight, with the infants requiring the higher relative perfusion rate. As cyanotic patients have an appreciable bronchial collateral, and consequent shunting of blood from the aorta to the heart, they will often receive as much as twenty per cent more blood during the perfusion than the acyanotic. The actual flow rate utilized for

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*Sigmamotor Inc., 3 North Main Street, Middleport, New York. Pumps used are Models T-65 and TM11.

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* Dow Corning Corporation, Midland, Michigan

† In patients where an unusually large blood loss may be anticipated we coat the cardiotomy reservoir with a thin film of Antifoam A

Anticoagulants

Twenty milligrams of heparin in 20 cc 5% dextrose is added to each 500 cc unit of blood The collection bottle should be rotated continually while the blood is being drawn to insure adequate mixing This amount of heparin is sufficient to inhibit clotting from the time of afternoon collection until it is to be used the following day The units of blood not used at the surgical procedure are returned to the blood bank where sodium citrate is added and the blood is taken over for general usage

Ordinary bank blood (collected in ACD solution) is used for blood replacement requirements up to the time of heparinization of the patient and insertion of the cannulae Immediately after the perfusion is concluded and protamine has been given the citrated blood is again used for all replacement needs

PREPARATION OF THE PATIENT

Weighing of the Patient

The patient is weighed accurately in the operating suite before being anesthetized and immediately after the operation. This has proven to be the most accurate and rapid method to ascertain the patient s blood volume immediately after the perfusion

Temperature Control

A water circulation blanket is used on the operating table to maintain the patient euthermic throughout the operation A constant recording rectal thermometer is used to monitor the patient s temperature while he is on the blanket and the thermal blanket is altered to the degree necessary to maintain the patient s temperature at the desired normal level

For successful clinical perfusions of any appreciable duration external heat must be applied to the blood circulating through the extracorporeal apparatus (1) to prevent a fall in the patient s body temperature with the consequent cardiac depressing effects of hypothermia and (2) to prevent air embolism If the blood in the pump oxygenator (whether it be bubble film or membrane type) is allowed to cool significantly it will release oxygen bubbles from the plasma upon entering the arterial system of the warmed

a particular patient depends upon the monitoring electroencephalogram and systemic blood pressure as indicated below.

Evaluation of the Perfusion

Electroencephalograms are monitored throughout the perfusion as are intraluminal arterial pressures by means of a polyethylene catheter in the internal mammary artery. If the electroencephalogram does not remain approximately the same as its preoperative tracing, the perfusion rate is increased until the electroencephalogram tracing has sufficiently improved.

BLOOD PREPARATION

Time for Blood Collection Prior to the Perfusion

Probably the best time for the collection of blood to be used for priming and replacement during a perfusion would be immediately prior to its actual use. In practice usually we have collected the blood the afternoon before the intended perfusion. This allows ample time for proper collection and unhurried crossmatching. After the blood is collected, it is stored in the usual blood bank refrigerator until time for its use.*

Conditions for the Collection of the Blood

The blood is drawn by gravity without vacuum into siliconized bottles. We feel that the frothing produced by the usual vacuum bottle is damaging. Sometimes "arterialized" venous blood[2] is drawn in an amount adequate to prime the oxygenator. This arterialized venous blood has the advantage of containing fewer acid metabolites than venous blood, especially if there is some stasis in the arm when the blood is drawn. However, carefully drawn venous blood arterialized in the oxygenator also is satisfactory for priming the oxygenator. The gain from using arterialized venous blood to prime the oxygenator may not be great enough to warrant the extra effort required to obtain it. The priming blood is intercross matched, while the remainder of the bottles are only crossmatched with the patient.

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* The Blood Bank at the University of Minnesota is under the direction of Newell Ziegler, M.D.

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patient In the system herein described the helix reservoir is immersed in a water jacket thermostatically controlled at 41° C

By these methods adequate temperature control has been regularly achieved for perfusions lasting more than one hour

Cannulations

A common femoral artery catheter will provide the easiest access to the patient's arterial system, and eliminates some of the dissection within the chest This vessel may occasionally be of insufficient size, especially in infants and in these patients the left subclavian artery can be used for the arterial cannulation Subclavian artery cannulations have the theoretic danger of producing turbulent jets of blood at the origins of the innominate or left carotid arteries and thus increasing the resistance to blood flow to the brain, however, we have never actually demonstrated this to happen If for some reason a right subclavian artery cannulation becomes necessary, the catheter should not be inserted far enough into the vessel to occlude the right common carotid origin The vena cavae catheters should be placed well into the cavae and have multiple fenestrations The cross-sectional area of the caval catheters should be about one-half the cross-sectional area of the cavae Larger caval catheters will prevent adequate atrial filling when the perfusion is not in progress, and smaller catheters may have unnecessary resistance to adequate drainage of the cavae during the perfusion

Heparinization of the Patient

Two and one-half to three milligrams per cent heparin in the circulating blood has proven to be a safe anticoagulation level for perfusions lasting up to ninety minutes Time intervals beyond this have not been investigated clinically If the circulating heparin during the perfusion is less than two milligrams per cent, the blood may clot after about twenty minutes The heparin level in the priming and replacement bottles is about four milligrams per cent (20 mgm /500 cc bottle) The blood volume of the patient can be estimated (10% of his body weight) and a quantity of heparin given to the patient to provide for him a heparin level after dilution by the priming blood of 2 5 to 3 0 mg % Therefore

the heparin dose given to the patient is dependent upon his size and the size of the reservoir For infants and children 1 5 mgm heparin per kg body weight will suffice while adults may require from 2 to 2 5 mgm heparin per kg body weight

Protamine Requirements to Neutralize Heparin

Adequate hemostasis in these patients after the procedure is a necessity as the heparinized patient may be expected to bleed more than an unheparinized patient undergoing a thoracotomy An empiric dose of protamine sulfate is given to the patient immediately after the perfusion This quantity is equal to two times the heparin dosage administered at the time of initial heparinization The final heparin level of the patient is somewhat higher than the amount initially given to him due to that added from the replacement blood and from the oxygenator

As soon as the chest tubes are placed prior to closure they are attached to a suction source This practice allows measurement

TABLE II

RESULTS IN LAST FORTY OPEN INTRACARDIAC OPERATIONS CONSECUTIVELY PERFORMED UTILIZING TOTAL CARDIOPULMONARY BYPASS, UNIVERSITY OF MINNESOTA 1957

Defect	*Number of Cases*	*Number Surviving*	*Age Years*	*Plasma Hgm Mgm %*	*Pump Time Minutes*	*Cardiac Arrest Time Minutes*	*Weight Kg*	*Perfusion Rates cc/kg/min*
Ventricular	14	14	2 to 18	20 to 45	18 to 40	3 to 18	10 to 71	42 to 78
			6.2	32	22	10	26.4	57
Tetralogy of Fallot	10	9	5 to 19	53 to 110	29 to 50	16 to 26†	12 to 51	50 to 75
			8.6	78	40	20	26.6	64
Atrial (Secundum)	8	8	8 to 27	20 to 63	16 to 27	not used	20 to 69	45 to 85
			18	40	19		42	60
Aortic Stenosis	3	3	8 to 22	12 to 40	14 to 20		21 to 73	41 to 57
			12.7	27	16		49	51
Mitral Regurgitation	2	2	19 to 30	60	22 to 29		43 to 58	52
			24.5	60	26		51	54
Atrioventricularis Communis	1	1	19		30		37	51
Single Ventricle	1	1	22	63	62		57.2	53
Isolated Infund Pul Sten	1	1	8	33	1		22.3	51
Total	40	39						

* Cardiac arrest used in 18 cases
† Cardiac arrest used in all cases

and replacement of blood which may collect while the chest is being further closed as well as to prevent coagulation and obstruction of the drainage catheters.

RECENT RESULTS

Over three hundred and fifty direct-vision intracardiac surgical procedures have been done at this hospital utilizing extracorporeal perfusion techniques. The results of the first 305 of these procedures have previously been reported.[4] The cases shown in Table II are the consecutive unselected cases done by the authors since this previous report. In these forty patients, all undergoing reparative surgery for a wide variety of congenital and acquired cardiac lesions using the apparatus and principles described above, there has been only one postoperative death, a mortality rate of 2.5%. It might be mentioned that six of these patients had total bypass procedures lasting one hour or more.

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THE STATIONARY VERTICAL SCREEN OXYGENATOR

By

JOHN W KIRKLIN, M D., RICHARD A THEYE, M.D ,
and ROBERT T PATRICK, M D

THE STATIONARY vertical screen oxygenator was devised by Gibbon and the original models were engineered by The Research Laboratories of International Business Machines The Section of Engineering of the Mayo Clinic made modifications in the design of the original Gibbon oxygenator and constructed the oxygenator herein described *† Details of the oxygenator described herein and data on its use and performance are not necessarily applicable to other available stationary vertical screen oxygenators of somewhat different design

DESCRIPTION

Each stainless steel screen is 30 5 cm wide and 61 cm long (Fig 22) The blood flows in a thin film down the screen and is exposed to the gaseous environment in the oxygenator From the upper oxygenator reservoir the blood is evenly admitted onto the top of each screen through a weir or slit which extends across the entire width of the upper edge of each screen (Fig 23) The weir is 1 6 cm deep and at present is 0 02 cm (0 008 inch) wide This change from the previously described width of 0 006 inch was made to obviate infrequent but distressing plugging of

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* The authors are but the spokesmen for those members of the staff of the Mayo Clinic who have built studied and employed this equipment This group includes in addition to the authors, Mr Richard E Jones Drs. David E Donald H J C. Swan, Earl H Wood and H Frederic Helmholz, Jr

† This oxygenator is now produced commercially by the Custom Engineering and Development Company 1427 1429 South Ewing, St Louis 4 Missouri.

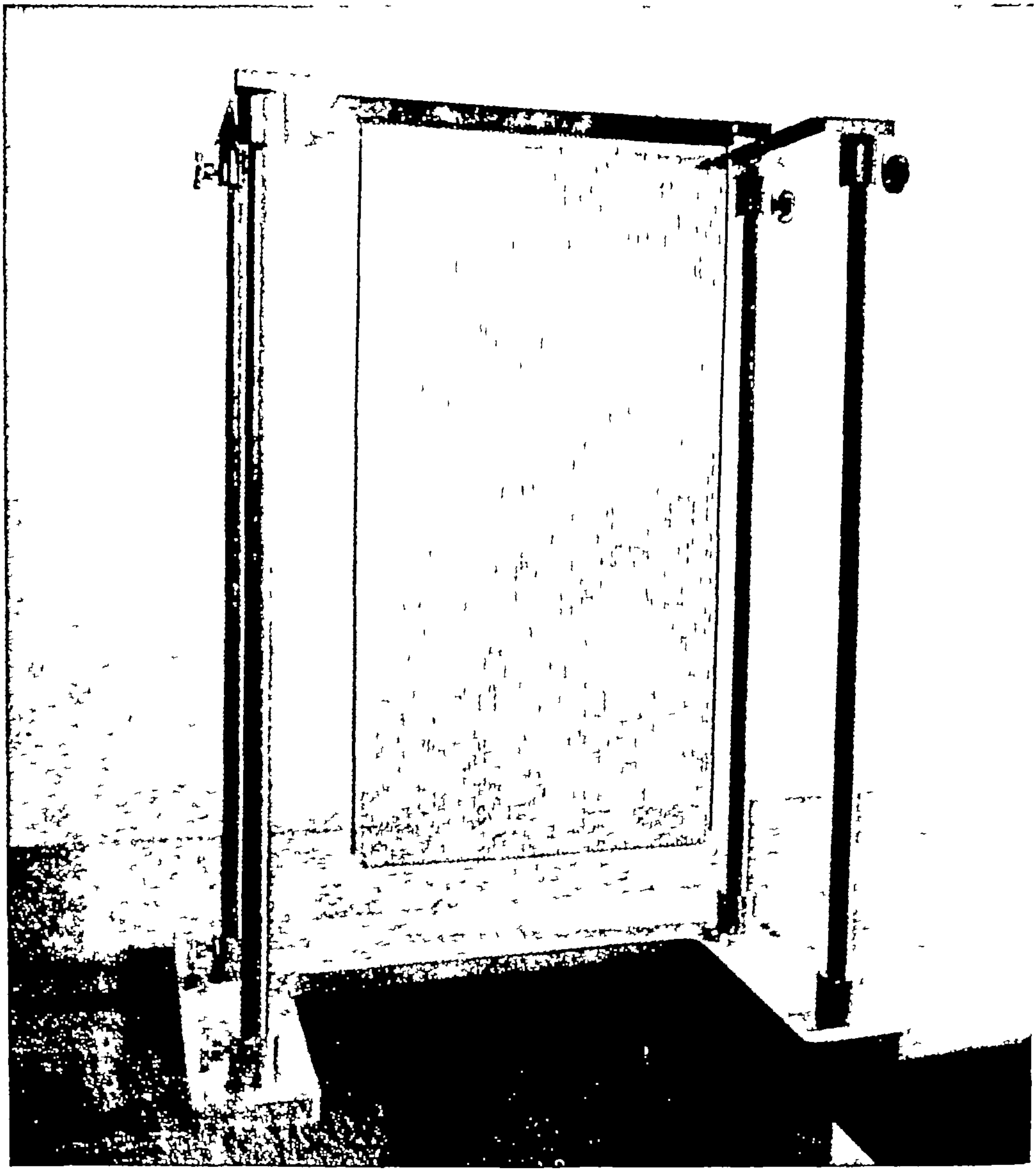


Fig 22 Single oxygenator screen

the wells during perfusion of polycythemic patients Blood passes from the bottom of the screens into the lower oxygenator reservoir A pump moves blood into the upper oxygenator reservoir at a desired rate of flow and the arterial pump withdraws its blood from the lower oxygenator reservoir

The screens and reservoirs are encased by a lucite housing (Fig 24) Attachments are provided for the admission of gas mixtures and their venting From three to fourteen screens may be used

The remainder of the flow circuit and the control devices of

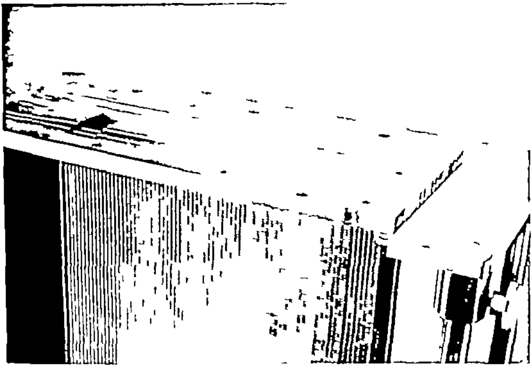


FIG 23 Top of screens showing the slits through which blood is admitted to the top of each screen

the modified Gibbon type pump oxygenator in which the described oxygenator is used are not pertinent to the present discussion Details of this have been published [1]

SPECIFICATIONS

Data regarding performance are given for an individual screen the basic unit of this oxygenator

Flow —Flows varying from 165 to 250 cc per screen per minute are employed Since from three to fourteen screens are used, the range of flow through this oxygenator is from 500 to 3500 cc per minute Although the oxygenator can be used with flows per screen outside the range used less satisfactory over all function of the oxygenator results

Oxygenation —One probable advantage of the vertical screen oxygenator is that its design is such that function of the oxygenator is susceptible to analysis on a physical and physiologic basis which in turn may lead to predictability of performance and optimal design Mr R E Jones of the Section of Engineering of

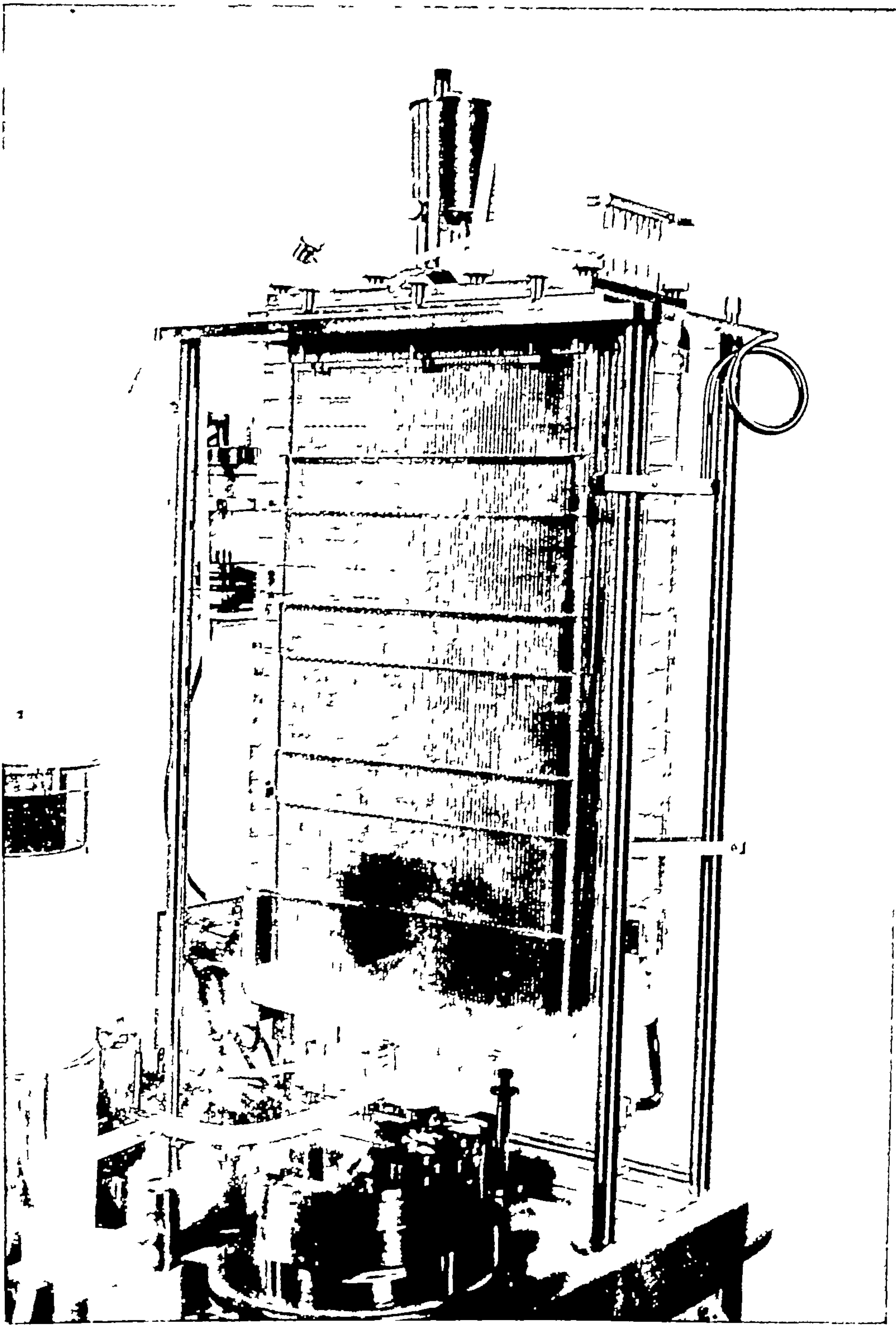


Fig 24 Assembled oxygenator

the Mayo Clinic has recently made such a theoretic analysis and the data obtained in our laboratories to date confirm his conclusions in a general way.

During whole body perfusion in human beings the arterial blood has always had an oxygen saturation of 95 to 100 per cent when measured by cuvette oximetry. Although the term "per cent saturation" is that most commonly employed for describing the state of oxygenation of blood after its extracorporeal circulation, it appears to us more desirable to express it in terms of oxygen tension at the temperature of the patient. Figure 25 relates per cent saturation to oxygen tension in whole blood. Data are available on the oxygen content of the blood leaving a screen under the conditions existing during clinical use. From these data oxygen tension can be estimated, although it has not as yet been actually measured by us (Table I). These studies support the belief that oxygen tension in the range between 100 and 250 mm. of mercury at the patient's temperature is obtained in blood which has passed once across a screen under the conditions obtaining during clinical use of the apparatus. These are as follows: hemoglobin content in the blood of 12 to 14 gm. per 100 cc., venous hemoglobin saturation of 60 to 80 per cent, arterial carbon dioxide tension of 29 to 40 mm. of mercury, arterial pH of 7.35 to 7.40, temperature

TABLE I

OXYGEN CONTENT OF BLOOD AFTER ONE PASSAGE ACROSS SCREEN*

Screen Flow Rate (cc./min.)	Venous Blood: Content (Volumes Per Cent)	Venous Blood: Capacity (Volumes Per Cent)	Venous Blood: Saturation, Per Cent	Arterial Blood: Content (Volumes Per Cent)	Arterial Blood: Capacity (Volumes Per Cent)	Arterial Blood: Oxygen Tension Calculated for 37° C. (mm. of Mercury)
150			73†	2 3	21 7	190
165	11 9	18 7	63	18 1	18 3	100
160	13 3	16 6	80	17 3	16 7	190
203			63†	22 2	22 4	110
203	12 8	16 0	80	16 7	16 1	190

* Gas flow was 9 5 liters per minute of oxygen and 0 3 liter per minute of carbon dioxide.

† Determined by oximetry.

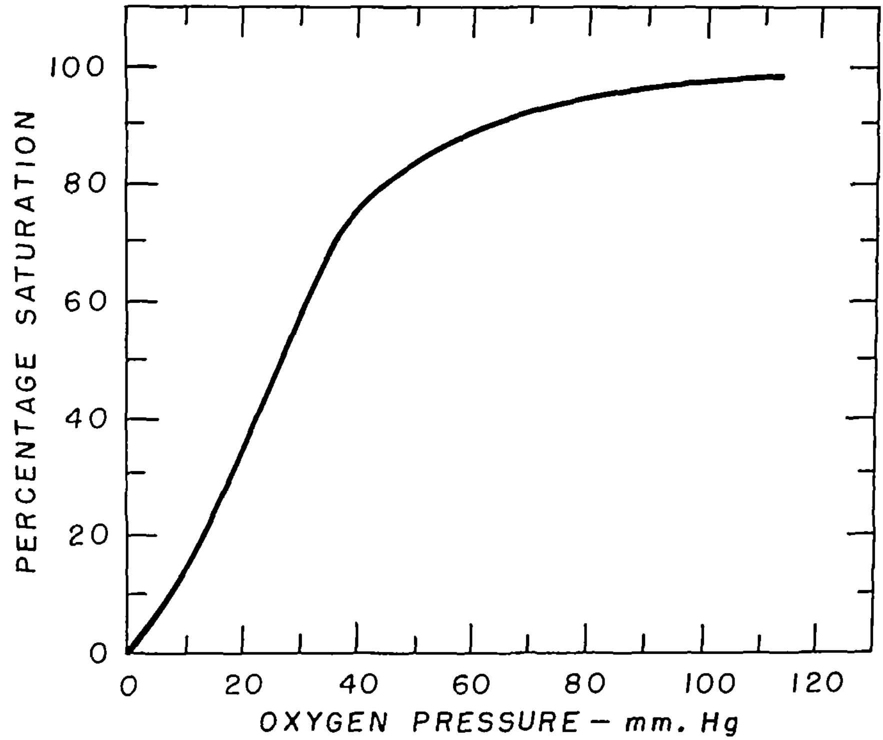


FIG 25 Oxygen dissociation curve of whole blood

within the oxygenator of 33 to 34° C, and patient temperature of 35 5 to 37° C

Carbon Dioxide Elimination.—Although the theoretic considerations underlying carbon dioxide exchange in the oxygenator have not been investigated, clinical experience indicates that elimination of carbon dioxide is adequate with this apparatus Gases are warmed and humidified before entering the oxygenator Gaseous flow into the oxygenator during perfusion consists of 9 5 liters of oxygen and 0 3 liter of carbon dioxide per minute This provides for a carbon dioxide pressure of 21 mm of mercury at a barometric pressure of 730 mm of mercury This is a change from the described original use of this oxygenator in which admittance of carbon dioxide to the oxygenator was automatically regulated by a pH meter In clinical cases, this system has never been used

Carbon dioxide tension in the arterial line during perfusion in human beings, corrected to 37 C, has been found to be between 29 and 40 mm of mercury

Blood Holdup —During use of this oxygenator 215 cc of blood are in the upper oxygenator reservoir and between 300 and 550 cc in the lower oxygenator reservoir depending upon the exact point of setting of the level sensing device Seventy cubic centimeters of blood are on each screen at a flow rate of 220 cc per screen

With three screens for small infants the holdup of the oxygenator is then between 725 and 975 cc of blood With eight screens to provide desired flow for a child seven years of age for example the holdup is between 1075 and 1325 cc of blood With fourteen screens for a large adult between 1500 and 1750 cc of blood are required to run the oxygenator

Trauma —Most commonly reported as indices of blood trauma are levels of hemoglobin in the plasma of blood which has traversed the apparatus and the incidence of abnormal bleeding

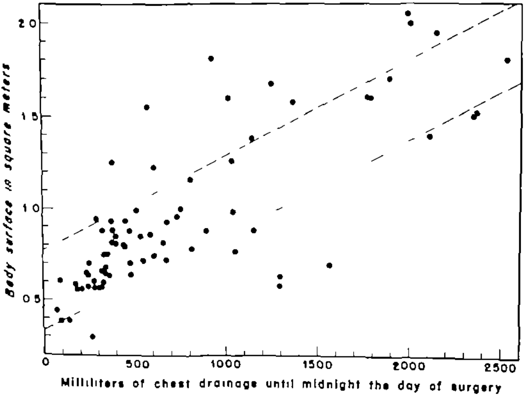


FIG. 26 Drainage (most of which is blood) through intercostal tubes in patients operated upon by means of the pump-oxygenator between January 1 and August 1 1957 No patients had significant drainage after 12 p.m on the day of operation

following operation in which the apparatus has been employed

Figure 26 presents data on drainage through the intercostal tubes from the end of operation until 12 p m (midnight) on the day of operation in all patients operated on in 1957 These losses are not considered excessive

Measurements of the concentration of hemoglobin in the

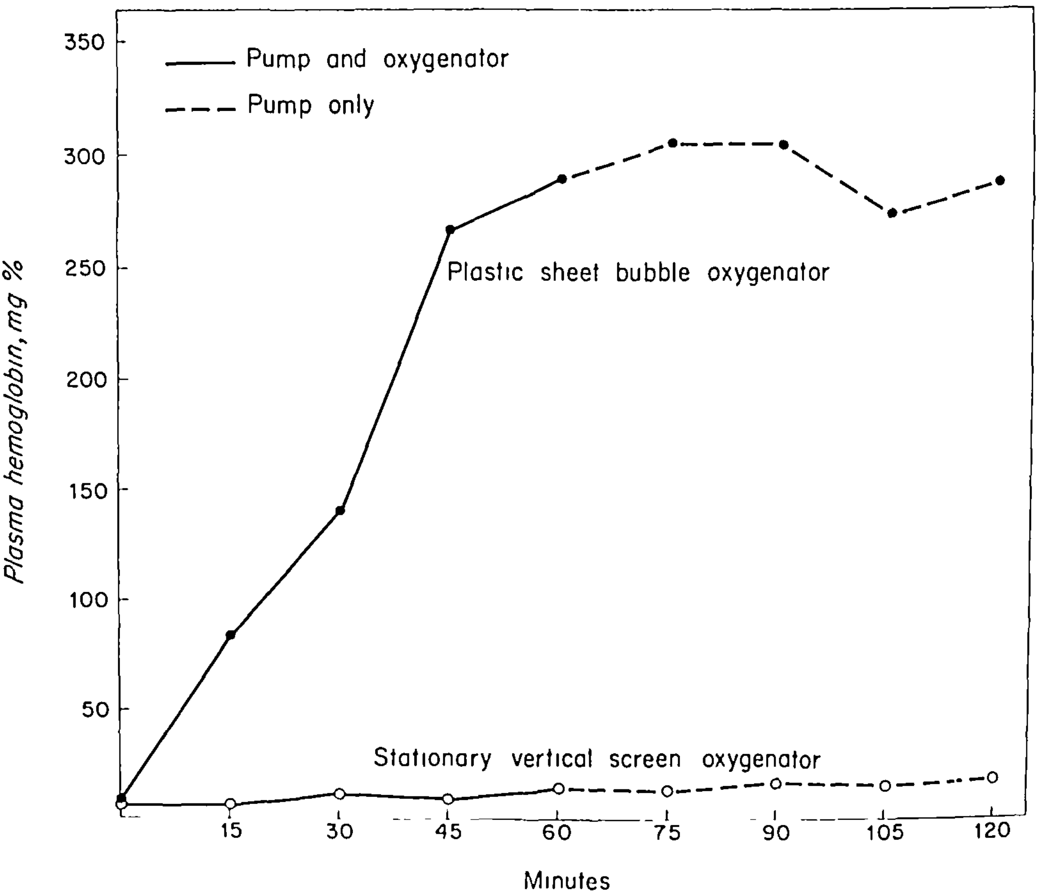


FIG 27 Concentrations of hemoglobin in plasma during the circulation of 2000 cc of dog blood through the stationary vertical screen oxygenator by a non-occlusive roller pump A flow rate of 220 cc per screen with five screens in the oxygenator was employed, giving a total oxygenator flow rate of 1100 cc per minute Concentrations of hemoglobin in plasma were determined during sixty minutes of circulation through the pump and oxygenator and then during sixty minutes of circulation by the pump without the oxygenator It is concluded that the oxygenator per se produced 9 mg of hemoglobin in plasma in one hour under these circumstances For comparison, similar measurements were made with the plastic bubble type oxygenator under similar circumstances except that the total oxygenator blood flow was 500 cc per minute

plasma during internal circulation through a pump and oxygenator without a subject in the circuit appear to give more information on trauma produced by the apparatus than do measurements during perfusion. In such an experiment carried out by Drs. D. C. McGoon and E. W. Ferbers in our laboratories, with details of the experiment as indicated in the legend for Figure 27, the concentration of hemoglobin in the plasma was elevated only 9 mg per 100 cc by passage of canine blood through the oxygenator for sixty minutes.

TECHNIC FOR USE OF OXYGENATOR

Lucite parts are sterilized by immersion in a 10 per cent solution of formaldehyde for two hours. Metal parts are autoclaved. Under aseptic precautions, the individually sterilized pieces are assembled prior to use of the oxygenator. In setting up the apparatus for a given perfusion the number of screens employed is determined from the surface area of the patient. Table II indicates the number of screens used for patients of varying surface areas, the flow per screen and the anticipated total perfusion flow (and thus total oxygenator flow).

TABLE II

NUMBER OF OXYGENATOR SCREENS AND FLOW RATES EMPLOYED FOR PATIENTS OF VARYING SURFACE AREA

Patient's Surface Area (sq. m.)	*Number of Oxygenator Screens*	*Oxygenator Pump Setting (Expected Flow) l./min./sq. m.*	*Ranges of Flow Per Screen* (cc./min.)
0.2 through 0.28	3	2.5	107–232
0.29 through 0.37	4	2.5	181–238
0.38 through 0.47	5	2.5	190–230
0.48 through 0.59	6	2.4	191–230
0.6 through 0.69	7	2.4	200–237
0.7 through 0.79	8	2.4	210–237
0.8 through 0.89	9	2.3	204–228
0.9 through 0.99	10	2.3	207–228
1.00 through 1.09	11	2.3	208–227
1.10 through 1.19	12	2.2	202–211
1.20 through 1.29	13	2.2	213–228
1.30 through 1.39	13	2.1	210–224
1.40 through 1.49	13	2.0	210–229
1.50 through 1.59	14	2.0	214–227
1.60 through 1.69	14	2.0	228–241
1.70 through 1.79	14	1.9	231–243
1.80 through 1.89	14	1.8	232–243
1.90 through 1.99	14	1.8	243–257
2.0 through 2.09	14	1.8	237–269

After the oxygenator has been filmed there is internal circulation of blood through the pump oxygenator prior to the establishment of whole body perfusion Data have been obtained which indicate that after three to five minutes of internal circulation during which time a gas mixture, 97 per cent of which is oxygen, has been passing through the oxygenator, an extremely high oxygen tension is present in the arterial blood Since this is believed by us to be undesirable, room air with approximately 3 per cent carbon dioxide added is passed through the oxygenator until perfusion is actually established On perfusion the gas flowing into the oxygenator consists of 9 5 liters of oxygen and 0 3 liter of carbon dioxide per minute

Before establishing whole body perfusion, the venous or recirculation pump is set for the rate of flow which the arterial pump is expected to deliver during complete cardiopulmonary bypass Consequently, when perfusion has been established there is ordinarily no recirculation within the apparatus and the recirculation line is completely closed by the occluder mechanism This is a change from the original description of the use of this apparatus As the equipment is now being employed, blood makes only one passage through the oxygenator before returning to the patient These conditions appear to us to be advantageous

REFERENCE

1 Jones, R E, Donald, D E, Swan, H J C, Harshbarger, H G, Kirklin, J W and Wood, E H Apparatus of the Gibbon type for mechanical bypass of the heart and lungs Preliminary report *Proc Staff Meet, Mayo Clin*, *30* 105-113, 1955

CHARACTERISTICS OF AN IDEAL OXYGENATOR

By

JOHN Y TEMPLETON, III, M.D

The term oxygenator is perhaps an inadequate one because it does not imply the exchange of carbon dioxide which is quite as important as that of oxygen Nevertheless its wide use makes it an acceptable designation for the equipment under consideration The diversity of the types of apparatus presently used to effect extracorporeal gas exchange indicates the lack of agreement as to the best means of accomplishing the purpose of the apparatus Nevertheless progress to this point permits description of some of the desirable characteristics of an ideal oxygenator Of the various types presently available many embody some of these characteristics but it will probably be some time before a single method has most of the desirable features Therefore it seems undesirable to attempt to standardize the method at this time

Gas exchange in the oxygenator should provide normal oxygen saturation and carbon dioxide content in the blood delivered to the patient At the same time normal levels of partial pressures of oxygen and carbon dioxide should be maintained in the arterialized blood In the interest of simplicity and safety gas exchange should take place at normal atmospheric pressure and changes in the pressure to which the blood is subjected should be minimal The temperature of the blood in the oxygenator should be that of the patient s body and water should neither be lost nor gained The advantages of a completely closed system without a gas liquid interface are evident Such a system in which gas exchange is accomplished across a membrane most nearly duplicates the function of the lungs which the oxygenator is designed to temporarily replace

The flow characteristics of the blood within the oxygenator

After the oxygenator has been filmed there is internal circulation of blood through the pump oxygenator prior to the establishment of whole body perfusion Data have been obtained which indicate that after three to five minutes of internal circulation during which time a gas mixture, 97 per cent of which is oxygen, has been passing through the oxygenator, an extremely high oxygen tension is present in the arterial blood Since this is believed by us to be undesirable, room air with approximately 3 per cent carbon dioxide added is passed through the oxygenator until perfusion is actually established On perfusion the gas flowing into the oxygenator consists of 9 5 liters of oxygen and 0 3 liter of carbon dioxide per minute

Before establishing whole body perfusion, the venous or recirculation pump is set for the rate of flow which the arterial pump is expected to deliver during complete cardiopulmonary bypass Consequently, when perfusion has been established there is ordinarily no recirculation within the apparatus and the recirculation line is completely closed by the occluder mechanism This is a change from the original description of the use of this apparatus As the equipment is now being employed, blood makes only one passage through the oxygenator before returning to the patient These conditions appear to us to be advantageous

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THE MULTIPLE SCREEN DISC OXYGENATOR

By

CLARENCE DENNIS, M.D., *and*
KARL E. KARLSON, M.D.

IN THE disc oxygenator the blood to be oxygenated is exposed to an oxygen containing atmosphere as a thin film upon one or more discs which revolve on a horizontal shaft. In the Bjork[1] pattern, formation of the film is accomplished by immersion of the bottom portion of each revolving disc in a river of blood, a technique which has proved effective for smooth surfaced discs. In the pattern of the author's group, a screen disc has been utilized to provide more efficient oxygenation through better mixing of blood in the film.[illegible] Immersion of such a disc is productive of foaming; we have therefore produced our film in a different manner, namely by laying blood by means of a low speed jet on the central solid portion of the screen disc.

Utilization of a screen to provide mixing in the film was the suggestion of Stokes and Flick[7] in Gibbon's laboratory. The pattern was modified by Miller, Gibbon and Gibbon,[8] who now utilize a stationary set of screens. Such a pattern as this poses a problem in creation of a smooth film at the start of each use of the oxygenator and necessitates that the flow be constantly maintained to prevent break-down of the film into a series of rivulets. It is for this reason that we chose first to evaluate, and then to use regularly, a revolving disc of screen. We have been pleased with the spontaneous filming of the screen disc we use and with the uniform maintenance of the film whether the flow is stopped periodically or not.

THE BJORK PATTERN

The smooth-disc type of oxygenator was first used by Bjork and Crafoord for perfusion of the brain during temporary occlu

should be such as to produce the least possible turbulence and the materials with which the blood comes in contact should have a minimum effect upon the formed elements of the blood and upon the various components of the plasma protein and enzyme systems

The apparatus should be capable of handling a blood flow equal to the normal cardiac output of the subject and the volume of blood within the oxygenator should be constant within the range of such flow rates Different sizes of apparatus would be helpful in most efficiently meeting the widely varied needs of patients of different ages and surface areas

The volume of blood required to fill the oxygenator should be as small as is consistent with adequate function The minimal blood requirement of a low volume apparatus would considerably lessen the burden of obtaining sufficient blood donors and would diminish the workload of cross-matching on the part of the transfusion unit personnel Proportionate reduction in the dangers of transfusion reaction and homologous serum jaundice would be obtained Simplicity in the apparatus is obviously advantageous It should have no moving parts, no recirculation flow should be required and it should be adaptable to operation by technicians of ordinary ability It should be easily and quickly assembled and capable of preparation and storage in a state in which it could be used with a minimum of time spent in preparation

The ease and reliability of heat sterilization as compared to cold make it highly desirable that the apparatus permit autoclaving, preferably after assembly is completed Ideally, the major parts with which blood comes in contact should be disposable after each use and there must be no question of the complete mechanical cleanliness of those components which are used repeatedly

A brief consideration of some of the characteristics of an ideal oxygenator has been given A disposable high flow, small volume, autoclavable, membrane oxygenator functioning at body temperature and atmospheric pressure with minimum turbulence would seem to most nearly meet the requirements

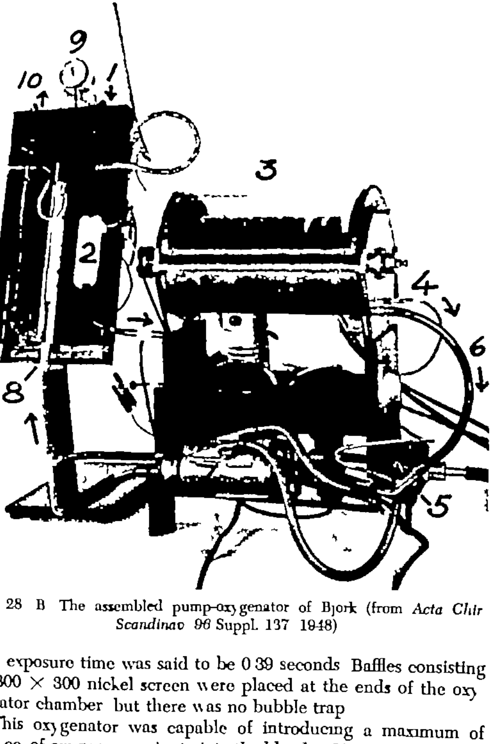


FIG 28 B The assembled pump-oxygenator of Bjork (from *Acta Chir Scandinav* 96 Suppl. 137 1948)

film exposure time was said to be 0 39 seconds Baffles consisting of 300 × 300 nickel screen were placed at the ends of the oxygenator chamber but there was no bubble trap

This oxygenator was capable of introducing a maximum of 110 cc of oxygen per minute into the blood at 1071 cc per minute of blood flow but it could not saturate blood at flows above 300 cc per minute The average oxygen uptake was 48 cc. of oxygen per minute at an average blood flow of 680 cc. Unfortunately the

sion of the vena cavae for cardiac surgery This oxygenator has subsequently been used with slight modification by Cross and Kay[2] for total cardio-pulmonary by-pass and intracardiac surgery The Bjork oxygenator consists of a series of forty stainless steel rhodium-plated discs, each 0 5 mm thick, 13 cm in diameter, and mounted in groups of four on a rotating horizontal steel shaft The discs are spaced on the shaft with 4 mm between discs and 8

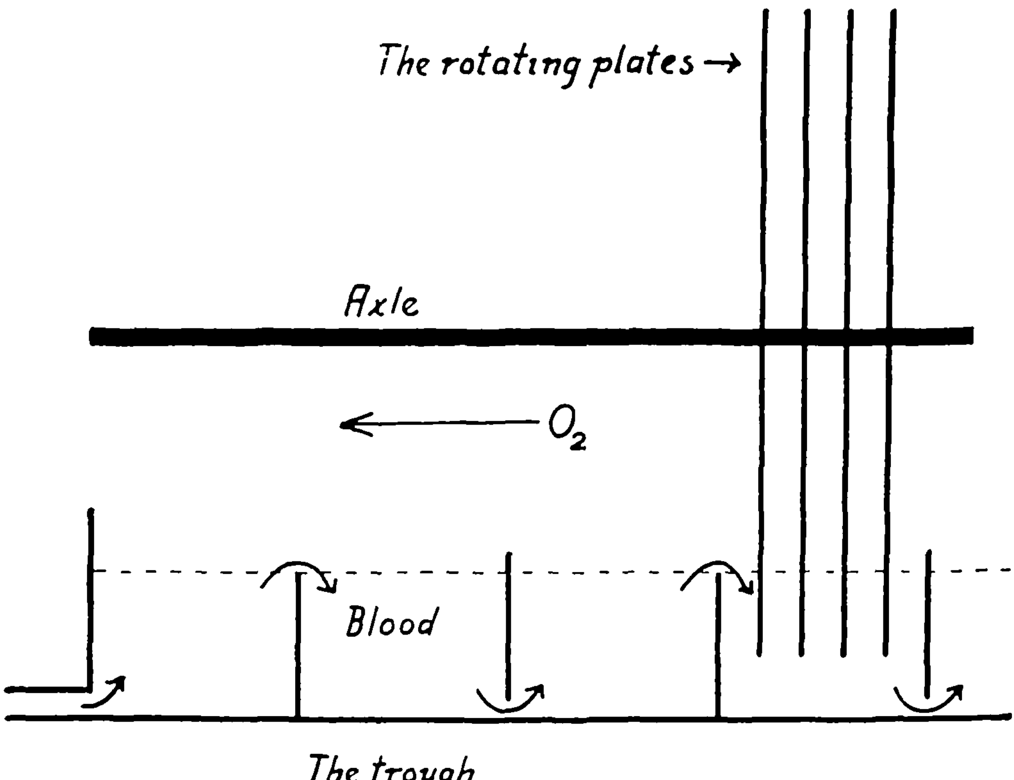


FIG 28 A Line drawing of pattern of Bjork oxygenator (Bjork *Acta Chir Scandinav 96* Suppl 137, 1948)

mm between groups of four (Fig 28A, B) The rotating discs dip into a river of the blood to be oxygenated, and mixing in the river of blood is assured by a series of baffles which match the 8 mm spaces between discs The plates rotate at 120 rpm and the blood content of the oxygenator is stated to be 250 cc The plates dip into the blood to a depth of 15 mm , providing an area of blood film of 0 37 sq meters exposed at any moment to the oxygen atmosphere The minute film area is 44 sq meters and the mean

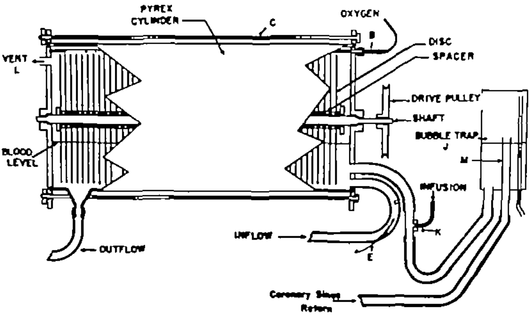


FIG 29 Diagram of the Kay-Cross version of the Bjork oxygenator (From *Proc Soc Exper Biol & Med 93* 210 1956)

oxygen per minute into the blood while the arterial oxygen content was 18 6 volumes % Hemolysis is from 10 to 160 mgm % in 30 minutes

OUR MODEL OF THE BJORK OXYGENATOR

In our laboratory a Bjork oxygenator was constructed corresponding as precisely as possible to the description which he provides except that the volume of blood was not as precisely held to a minimum as Bjork succeeded in doing Our experience with the Bjork oxygenator indicated to us that foaming was frequently a problem that hemolysis was occasionally excessive and that oxygenation was not as effective as we had hoped probably because of the larger volume in our model of the apparatus Our model held 730 cc of blood as compared to Bjork s 460 cc and introduced 36 6 cc of oxygen per minute at a flow rate of 500 cc

OUR OXYGENATOR

The first vertical rotating disc oxygenator which was developed in our laboratory was designed to increase the area of film by use of much larger discs and a blood jet to film those discs placed so as to play blood near the center It consisted of rotating stain

per cent oxygenation of the arterialized blood at these flows is not given in Bjork's paper The plasma hemoglobin level increased in recirculation an average of 168 mgm % in three hours In brain perfusions of dogs, the hemolysis was variable, but the mean rise was 152 mgm % in two hours The white blood cell count decreased an average of 30% in two hours with a relative increase in lymphocytes

The limited oxygenating capacity of this apparatus led to a modification which was designated by Bjork as the "large" oxygenator It consisted of 50 discs, had a blood content stated to be 400 cc and a minute area of blood film exposed to oxygen of 77 sq meters This "large" oxygenator introduced a maximum of 131 cc of oxygen per minute into the blood at a flow rate of 800 cc per minute The average oxygen uptake with this apparatus was 90 cc of oxygen per minute at an average flow rate of 762 cc per minute Again, the per cent saturation of the arterialized blood is not given, although it was considered by Bjork to be adequate

THE CROSS-KAY MODIFICATION OF THE BJORK OXYGENATOR

The modification of this oxygenator which is used by Cross and Kay[2] is constructed of 59 Teflon-coated stainless steel (or entirely Teflon) discs, 0 4 mm thick and 12 2 cm in diameter These discs are mounted 5 mm apart on a horizontal shaft and enclosed in a cylinder of silicone-coated pyrex glass (Fig 29) Fourteen hundred cc of blood is introduced, and the discs dip into the blood pool to a depth of 4 1 cm With this arrangement, 0 84 sq meters of disc area is exposed to oxygen at any one time With 120 rpm, 110 sq meters of blood film is exposed to oxygen per minute The oxygen flow is five liters per minute through the apparatus and oxygen is warmed before introduction No bubble trap or filter is used

This oxygenator is capable of introducing a maximum of 207 cc of oxygen per minute into the blood During actual perfusion at 2000 cc per minute blood flow and an arterio-venous oxygen difference of 6 8 volumes %, the apparatus introduced 136 cc of

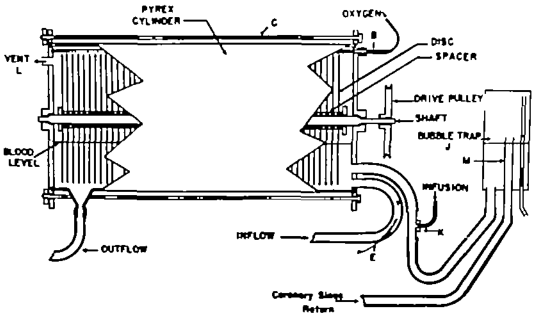


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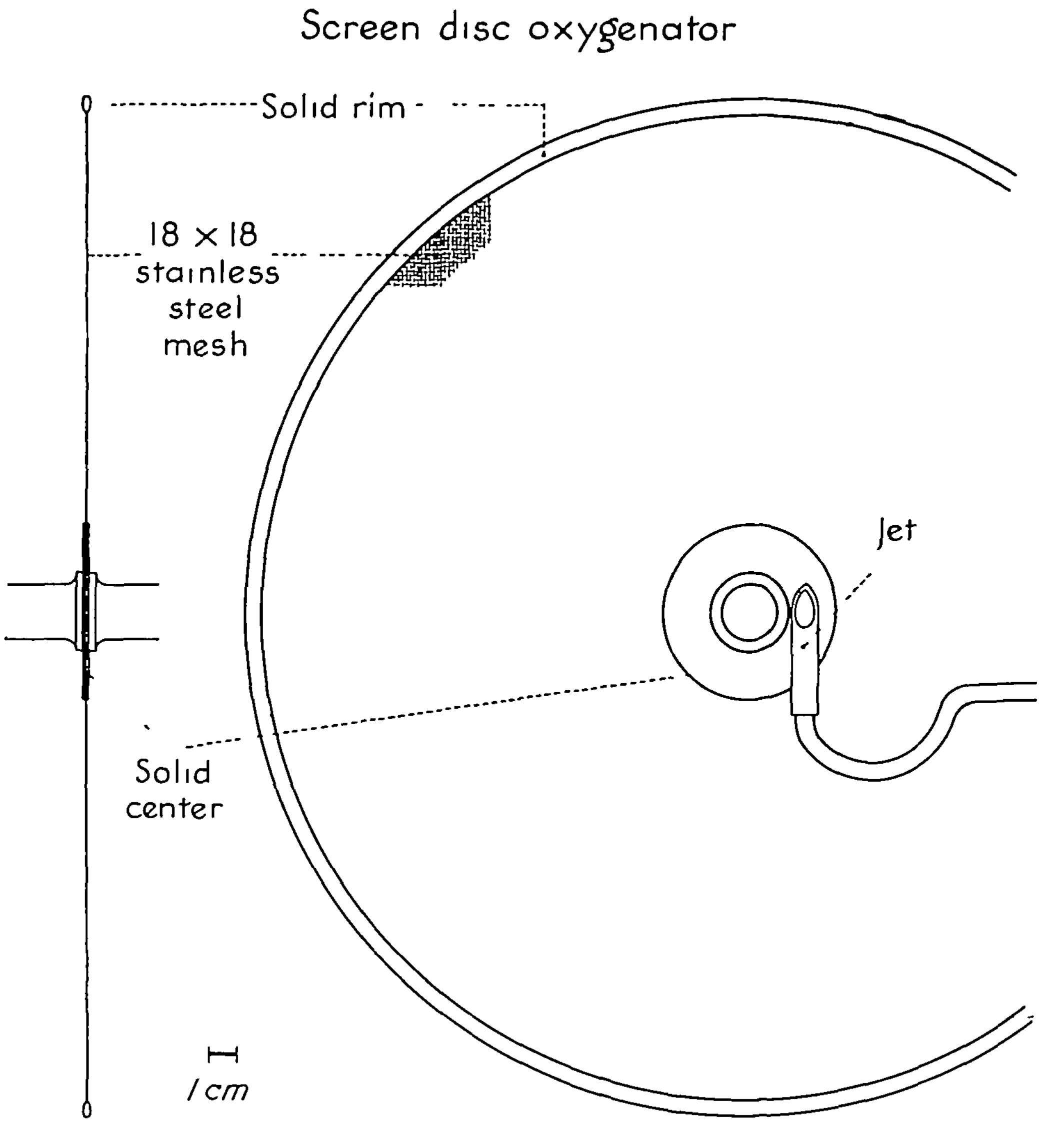


FIG 30 Artist's drawing of the screen disc (From *Ann Surg 134* 709, 1951)

less steel discs mounted on a horizontal shaft The discs were of several sizes up to 38 cm in diameter The venous blood formed a film over the discs, and centrifugal force and gravity caused the blood in the film to progress toward the periphery of the disc, it then dropped a few millimeters from the inferior margin into a collecting reservoir (Fig 30) Several of these discs were mounted on a horizontal shaft in an oxygen atmosphere The oxygenating efficiency of this pattern was determined with varying types of discs, various sizes of discs and at varying rates of rotation

It was determined that a stainless steel screen disc made of

18 × 18 mesh stainless steel made of wire 0 009 inch in diameter was more efficient in oxygenating blood in this manner than were smooth discs or discs made of screening of finer or coarser mesh or of other wire diameter It was also shown that in order to get adequate oxygen uptake a 38 cm stainless steel screen disc was the minimum acceptable The oxygenating capacity of a single such disc rotating at 55 rpm was 23 cc of oxygen per 500 cc of blood flow per minute The volume of blood contained in the film on such a disc at any given moment at this blood flow was 60 cc

Initial studies with this technique indicated a very high rate of hemolysis which appeared at first to render the possibilities of the technique very limited It became apparent however that a solid rim of carefully smoothed metal as a margin for the disc reduced the hemolysis produced by this portion of the apparatus to a very acceptable level

The changes in various blood constituents other than the red blood cells were determined during 32 complete cardiopulmonary by pass procedures with an apparatus utilizing a multiple disc oxygenator on this pattern * These are shown in Table I An oxygenator of this pattern having eight discs of 38 cm diameter was utilized in the perfusion of our first two clinical patients in 1951

TABLE I

ACUTE METABOLIC CHANGES IN THE SCREEN DISC OXYGENATOR MEAN OF 32 TOTAL BODY PERFUSIONS IN DOGS

	Pre Perfusion	*After 45 Minutes of Perfusion*
pH	7 38	7 38
pCO_2	35 mm. Hg	27 mm Hg
CO_2 content	15 7 m.eq /l	14 5 m.eq /l.
Blood buffer base	44 m.eq /l.	40 m.eq /l
Serum Cl^-	108 m.eq /l	117 m.eq /l.
PO_4^{---}	4 0 mg /100 cc.	4 2 mg /100 cc
Pyruvic acid	1 7 mg /100 cc	2 4 mg /100 cc.
Plasma Hgb	40 mg /100 cc	80 mg /100 cc
Hematocrit	45%	40%
Hgb	12 8 gm. %	12 2 gm. %
Total protein	5 5 gm %*	4 8 gm %
Albumin	2 3 gm %	2 2 gm %
WBC	13 000 mm	5 000/mm.^{3}

3 5% CO_2 in oxygen surrounding discs

* This value is low because of dilution by glucose solution left after rinsing out formaldehyde used for sterilizing during 1951 and 1952

Neither patient survived, the first being lost because of our failure to be familiar with the anatomy of persistent atrio-ventricular canal and the second being lost because of a human failure in that the control circuit for the arterial pumps was not switched on by the operator at the beginning of the perfusion, and the pumps raced, exhausted the reservoir, and flooded the aorta with oxygen

Continued studies indicated that a disc of larger diameter is more efficient It was found that a single 50 cm screen disc mounted as before introduces 36 5 cc of oxygen per minute at a flow rate of 500 cc per minute The film volume per disc at this flow rate is 97 cc The rate of rotation of the disc with the larger screen could be reduced to 20-24 rpm without changing the film volume, oxygenating characteristics, or hemolysis

The oxygenator which we presently use, therefore, is constructed of four 50 cm stainless steel screen discs on a horizontal shaft which rotates at 23 rpm (Fig 31A, B) The pattern of the discs and the jets for provision of blood and oxygen are indicated in Figure 30 The four-disc unit is mounted in an enclosed chamber,

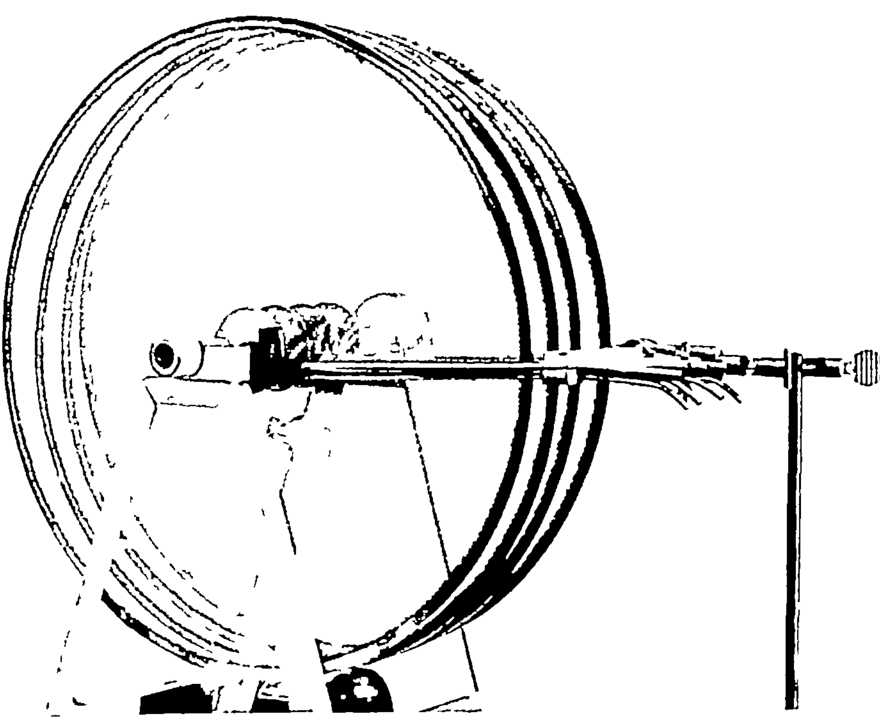


Fig 31 A Photo of mock-up of oxygenator, without the sheath and reservoir

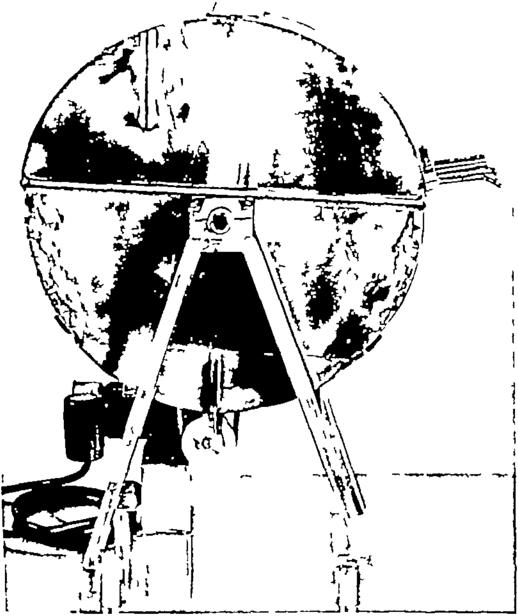


FIG 31 B The assembled oxygenator

the bottom of which serves as a reservoir for the oxygenated blood as it drops from the discs The blood volume of this apparatus utilizing four discs with a flow rate of two liters per minute is 988 cc of which 600 cc is in the reservoir and the remainder is in

the film. Oxygen is run into the tank through four jets adjacent to the blood jets at a rate of 10 liters per minute. The average oxygen uptake at two liters per minute flow is 146 cc. per minute, Fig. 31A.

The hemolysis with this oxygenator is minimal, the average being less than 100 mg. % increase during an hour of perfusion. No filter as such is used, but a bubble trap has been designed in the laboratory, utilizing stainless steel sponge treated with silicone. This is a precautionary measure should the tank level inadvertently be carried too low, and it furthermore serves as a rather effective filter for particulate matter.

CRITERIA FOR EVALUATION OF OXYGENATORS

An objective measure for the quantitative evaluation of the efficiency of oxygenators appears to be valuable. We suggested in 1949 the definition of oxygenator efficiency as that volume of oxygen introduced per minute for each 100 cc. of blood required to prime the oxygenator.[4] This is an incomplete measure inasmuch as it does not take into account the increase in oxygen per cent saturation accomplished by one passage of blood through the oxygenator or the completeness of saturation of the "oxygenated" blood. If one specifies that the oxygenator should add a minimum of seven volumes % of oxygen to the blood and bring it to a point close to full saturation, then this definition of efficiency is useful. Comparison of various reported oxygenators on this basis is difficult because of the inadequacy of data provided in many publications.

Table II presents data relative to the performance of the 38 cm. screen oxygenator disc as compared with the 50 cm. screen oxygenator disc. The efficiency of these two discs is seen to be the

TABLE II

RELATIVE PERFORMANCE OF TWO SIZES OF SCREEN DISC OXYGENATOR AT FLOW RATE 500 ML./MIN.

	Efficiency of Disc	*Efficiency Whole Unit*	*Increase Oxygen % Saturation*	*Oxygen Added Per Minute Per Disc*	*Film Volume on Each Disc*	*Hemolysis mg. %/hr. in Dog Perf.*
38 cm.	37	14.4	4.6	23 cc.	60 cc.	<100
50 cm.	37	14.8	7.3	36.5 cc.	97 cc.	<100

TABLE III

PERFORMANCE FACTORS IN SEVERAL TYPES OF DISC OXYGENATOR

	Vol of Content (cc)	Oxygen Uptake (cc/min)	Flow (cc/min)	Plasma Hgb (mgm %)	Efficiency†
Bjork					
"small"	250	18	980	90/2 hr	10 2*
"large"	400	90	762		20 0*
Dennis	730	37	500	high	5
Cross and Kay	1400	136	2000	10–160/½ hr	9 7
Dennis	988	146	2000	<100/1 hr	14 8

* Not fully saturated

† cc oxygen added per minute per 100 cc of blood in oxygenator

same but the smaller one provides an inadequate rise in oxygen saturation in a given passage whereas the larger is adequate Hemolysis is minimal in both

Table III presents information concerning Bjork s small and large oxygenators and our model of the Bjork apparatus together with data concerning that of Cross and Kay and of the apparatus which we are presently utilizing Use of this means of making comparison appears to us to favor that apparatus currently in use in our laboratory

Other factors of importance in relation to evaluation of oxygenators are related to the ease of manufacture the durability the ease of cleaning and the certainty of sterilization The four disc screen oxygenator can be taken apart, cleaned assembled completely and packaged for autoclaving by one person in a period of fifteen minutes

Finally the risk of total body perfusion which has impressed us most is that of air embolization. This is a risk which is apparently eliminated provided only that the reservoir level to which the blood drops is within a few millimeters of the bottom edge of the discs

CONCLUSION

We are highly pleased with the performance of the rotating screen disc oxygenator described herein It is efficient easily cleaned and sterilized and not productive of air embolism It has been used regularly in over 1000 successful animal perfusions

It has been utilized in a series of clinical cases, the first in 1951, and the earliest successful one in June, 1955

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THE MEMBRANE OXYGENATOR*

By

G. H. A. Clowes, Jr., M.D.,† *and*
W. E. Neville, M.D.

A practical blood oxygenator dependent upon the diffusion of carbon dioxide and oxygen through thin plastic membranes has been developed and tested. Clinical use has proven it capable of supporting the circulation of adult man. Not only is it the purpose of this paper to describe this apparatus and its operation but to summarize some of the earlier work on the application of principles of diffusion and flow which led to its present stage of development.

In 1954 it became apparent that a large bubble oxygenator developed in our clinic[1] was producing emboli, both gaseous and particulate, which resulted in no survival of dogs subjected to total perfusion for periods greater than one hour. Despite the outstanding success of Lillehei and his associates using the bubble oxygenator of DeWall[2] and that of Kirklin *et al.*[3] using the Gibbon filming type oxygenator, it seemed advisable to devise a method for protecting the blood from direct exposure to gas as is done in the naturally occurring lung or gill. Not only is denaturation of protein known to occur at a gas fluid interface,[4] but such a closed system offers the advantages of a fixed fluid volume and positive return of blood to the organism without danger of entraining bubbles of gas during perfusion.

Mustard[5] and later Campbell[6] have shown that it is possible to use heterologous lungs for such purposes. However, certain disadvantages such as pulmonary edema occurred rendering them

* This project was supported in part by a grant from the Cleveland Area Heart Society.

† From the Department of Surgery, Western Reserve University School of Medicine at City Hospital of Cleveland, Cleveland 9, Ohio.

less effective. Early in their experience with the artificial kidney Kolff and Berk[7] observed that oxygen could be introduced into the blood flowing through the membranes if oxygen were blown into the apparatus. Using a modification of the Inouye artificial kidney,[8] Kolff and Balzer[9] demonstrated that the circulation of dogs could be supported with an artificial lung built of coils of thin polyethylene tubing. Although it functioned effectively it had the great disadvantage of trapping large volumes of blood, between 270 and 500 cc. for an effective surface area of 1.4 square meters of surface area.[10] This was capable of oxygenating about 75 cc. of venous blood per minute.

Since it was readily apparent that the limiting factor in the effectiveness of a membrane oxygenator was the speed of diffusion of gases through the membrane, Clowes, Hopkins, and Kolebow[11] studied the rate of oxygen diffusion into blood through a variety of membranes. The next problem was to devise an apparatus in which to employ the best of these membranes in such a fashion as to trap a minimum volume of blood flowing between the greatest possible area of the membranes. Using a variety of models this was worked out, and a multilayer apparatus was constructed capable of supporting the circulation of a dog.[12] This trapped about 140 cc. of blood per square meter of membrane area. Further development has gone on,[13] greatly improving the apparatus both with regard to priming volume, efficiency of gas transmission, and ease of assembly and operation.

The results to be presented are divided into three parts. The first deals with gas permeability of membranes, the second with the principles governing the efficiency of a membrane oxygenator and its development, the third with its use experimentally and clinically.

DIFFUSION OF OXYGEN THROUGH PLASTIC MEMBRANES

Although extensive work has been done on the dry and moist gas diffusion through various plastic films, to test plastics it is necessary to deal with them under conditions like those in the use to which they will be put. Therefore, the rate of oxygen diffusion into venous blood at a temperature of 33 C. to 34 C. was used as a method for comparison. This was accomplished in a

TABLE I

RATE OF OXYGEN DIFFUSION THROUGH PLASTIC MEMBRANES INTO VENOUS BLOOD

Membrane	*Thickness (Inches)*	*C C O_2/Sq Meter/Min.*	
		Variation	*Average*
Polytetrafluorethylene (Teflon)	0.00025	28.2–34.0	31.4
	0.0005	23.1–28.3	25.5
	0.001	15.3–18.2	16.7
Ethylcellulose	0.001	7.0–13.1	11.4
	0.003	3.7–5.2	4.3
Polyethylene	0.0008	6.2–8.9	8.2
	0.001	6.3–8.1	7.0
Cellophane	0.001	7.0–7.7	7.4
	0.003	5.1–6.9	6.0
Polyvinylchloride	0.005	1.1–1.6	1.4
	0.010	0.6–0.72	0.7
Polystyrene	0.001	2.0–2.8	2.5
Mylar	0.0002	0.4–1.0	0.5
Chlorinated rubber	0.0004	0.1–0.6	0.4

diffusion chamber in which the membrane of known area separated a given volume of blood on one side from flowing oxygen on the other Agitation of the apparatus assured good mixing Samples of the blood were taken at known intervals for determination of oxygen content by the method of Van Slyke To be sure of maximum diffusion measurements were made on the steep part of the dissociation curve and compared by the formula

$$\text{c c } O_2 \text{ diffusion/sq M surface area/min.} = \frac{\Delta O_2 \text{ content (vols \%)} \times \text{volume blood} \times 100}{\text{surface area membrane (sq cm)} \times \Delta T \text{ (min.)}} \quad (1)$$

In Table I are given data indicating that of the available films tested Teflon (Polytetrafluorethylene)* is superior to others in its oxygen permeability Use of this material was suggested by Clark,[14] and has recently been manufactured in thin films as yet not in sheets large enough to use for the full size oxygenator The 0.25 mil Teflon is too flimsy but in small models the 0.5 mil

* Kindly supplied by Dilectrix Corporation Farmingdale L.I., New York.

less effective. Early in their experience with the artificial kidney Kolff and Berk[7] observed that oxygen could be introduced into the blood flowing through the membranes if oxygen were blown into the apparatus. Using a modification of the Inouye artificial kidney,[8] Kolff and Balzer[9] demonstrated that the circulation of dogs could be supported with an artificial lung built of coils of thin polyethylene tubing. Although it functioned effectively it had the great disadvantage of trapping large volumes of blood, between 270 and 500 cc. for an effective surface area of 1.4 square meters of surface area.[10] This was capable of oxygenating about 75 cc. of venous blood per minute.

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Although extensive work has been done on the dry and moist gas diffusion through various plastic films, to test plastics it is necessary to deal with them under conditions like those in the use to which they will be put. Therefore, the rate of oxygen diffusion into venous blood at a temperature of 33° C. to 34° C. was used as a method for comparison. This was accomplished in a

sulted in poor oxygenation, for blood was exposed to a small proportion of the membrane surface.

Support of the plastic membranes to cause the formation of many small channels and consequent good distribution of blood over the surface was accomplished in two fashions. The first method depended upon causing blood to flow along wire mesh with membranes held in apposition on either side by oxygen pressure on the outside. This was highly efficient but had the serious disadvantage of admitting bubbles of gas to the blood through any pinholes that existed in the plastic. At the same time it was observed that tiny masses of fibrin tended to form on the mesh. These difficulties at once defeated one of the prime objectives of the membrane oxygenator.

Thereafter, work was directed to creating methods for support of the membranes from the outside by either screens or grooved surfaces of hard rubber. It was determined that blood could be made to follow channels by distending the membranes into grooves in the outside supporting plates. Observation of blood distribution was accomplished through a transparent acrylic plate clamped over a single membrane and grooved surface. Using polyethylene 0.8 mil in thickness, grooves 1/16 inch deep and 1/8 inch from ridge to ridge proved to be the best in this regard.

Resistance to flow increased by a factor of approximately 1.6 of the distance the blood was made to flow through the membrane. As the resistance rose, the increased pressure caused the membrane to stretch and a greater volume of blood was trapped in proportion to the surface of membrane to which it was exposed. This roughly followed a linear progression of 1.4 of the length of flow.

A larger oxygenator containing a pair of membranes was constructed with an oxygenating surface of 0.5 sq. meter. It contained grooves on each side set at 60° to each other. By introducing large grooves down the sides, blood distribution was made possible so that it could flow across the short dimension of the surface which greatly reduced resistance for area of exposure. Both polyethylene and ethylcellulose were found to transmit oxygen at a rate of 67 to 78% of the maximum expected values given in Table 1. At a rate of 100 cc. per minute oxygenated blood was pumped

material has strength more than twice that of 8/10 mil polyethylene and a permeability to oxygen 3.2 times as great. Its stretch characteristics are almost the same as this polyethylene.

Next in order of effectiveness was ethylcellulose 0.001" in thickness. This material proved unsatisfactory despite its good oxygen transmitting characteristics. The presence of pinholes caused leaks of dangerous proportions when in operation.

Polyethylene has been used up to the present time as the standard material for the membrane oxygenator. It is smooth, soft, and because of its stretchability does not easily rupture or tear. Furthermore, it is easily sealed or perforated by heat. The film despite initial nonwettability eventually is wet slightly, and a very thin film of protein material becomes deposited on the surface after long exposure to blood. Apparently this does not affect oxygen diffusion materially.

Carbon dioxide was found to diffuse from blood through Teflon, ethylcellulose, polyethylene, and cellophane at rates proportional to oxygen uptake. With Teflon carbon dioxide normally fell to values between 35 and 40 mm. of mercury partial pressure by the time blood had attained 85% oxygen saturation. With polyethylene this value was slightly higher, pCO_2 being equal to 40 to 45 when oxygen saturation reached 85%.

DEVELOPMENT OF A MEMBRANE OXYGENATOR

A variety of small models were constructed to learn what part is played by flow rate, resistance, and blood volume in exposing the blood to a given membrane area. Venous blood from a heparinized dog was pumped into the apparatus between the layers of membrane and made to flow at a known rate by Sigmamotor pumps.* The oxygenated blood coming from the apparatus was returned under pressure to the carotid artery in such a fashion that the brain was perfused. These procedures were carried on for a minimum of one hour and usually longer.

Attempts at making blood film between unsupported membrane layers proved disappointing. Under these conditions blood tended to run in large rivulets due to surface tension. This re-

* Supplied by the Sigmamotor Corporation of Watertown, N.Y.

sulted in poor oxygenation for blood was exposed to a small proportion of the membrane surface

Support of the plastic membranes to cause the formation of many small channels and consequent good distribution of blood over the surface was accomplished in two fashions The first method depended upon causing blood to flow along wire mesh with membranes held in apposition on either side by oxygen pressure on the outside This was highly efficient but had the serious disadvantage of admitting bubbles of gas to the blood through any pinholes that existed in the plastic At the same time it was observed that tiny masses of fibrin tended to form on the mesh These difficulties at once defeated one of the prime objectives of the membrane oxygenator

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from this device into the carotid arteries of dogs for periods of one to four hours without evidence of brain damage as indicated by lack of electroencephalographic depression and full recovery

A multiple layer oxygenator[12] was constructed using this principle which gave a much larger surface area In practice this was cumbersome because of an external manifold system used to distribute blood and oxygen to each unit Approximately 180 cc of flowing blood were trapped for each square meter of membrane area when polyethylene membrane 0 8 mil in thickness was used

THE MEMBRANE OXYGENATOR

The oxygenator at its present stage of development is illustrated in Figure 32 A variable number of units are employed depending upon the surface area required to furnish an adequate volume of oxygen per minute The supporting plates, illustrated in Figure 33 have a grooved surface on the upper side and a plastic screen mesh on the lower These are surrounded by a soft rubber

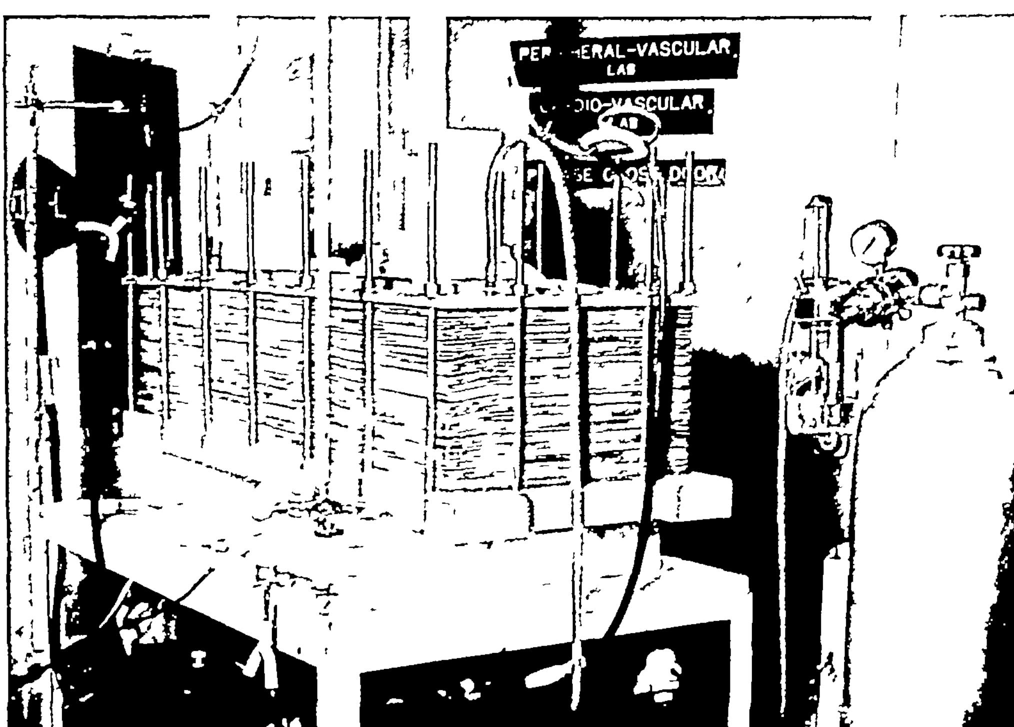


FIG 32 The assembled oxygenator, fifty units with a surface area of twenty-five square meters for perfusion of an adult woman

gasket to prevent leakage from the ends or sides of the blood held inside the pair of membranes placed between each of the supporting plates Blood which enters at one corner distends the membrane into the large ¼ groove and flows along the long side of each oxygenating surface As the pressure is increased the blood then distends the membranes into the little grooves which run across each supporting plate These are ⅛ inch from ridge to ridge Finally the oxygenated blood collects in the channel on the opposite side of the supporting plate and leaves each unit by the corner diagonally opposite to that which it entered.

Blood is distributed by a series of rings (inside diameter ⅜) with four side holes (1/16 in diameter) These are placed one above another between the layers of membrane as the apparatus is assembled and fit into the holes marked B in Figure 33 When the requisite number of units is assembled the membranes are pierced by passing a heated rod down through the column of rings Thus blood can be fed to all units simultaneously through a single inlet at the top of the apparatus The outlet for the blood is managed in exactly the same fashion

Oxygen flows in the grooves and screens on the outside of the membranes It reaches these through little channels cut on the back of the grooved surface so as to communicate with each groove One of these runs down each side of the supporting plates permitting gas to enter through one pass across through the grooves and screens and exit through the other A small tube communicates with one end of each oxygen distributing channel. Those at the inflow end enter a ¼ diameter hole marked "O" in Figure 33 These are superimposed as the apparatus is assembled and permit distribution of oxygen to all layers through an inlet at the top

Assembly is rendered easy by alignment posts set in the base plate seen in Figure 32 protruding through the top plate Each supporting plate has a pair of holes which fit over the alignment posts This ensures that the oxygen and blood inlet holes are accurately superimposed

Sterilization is accomplished by the introduction of Warexin *

* Supplied by Guardian Chemical Company Long Island City N Y

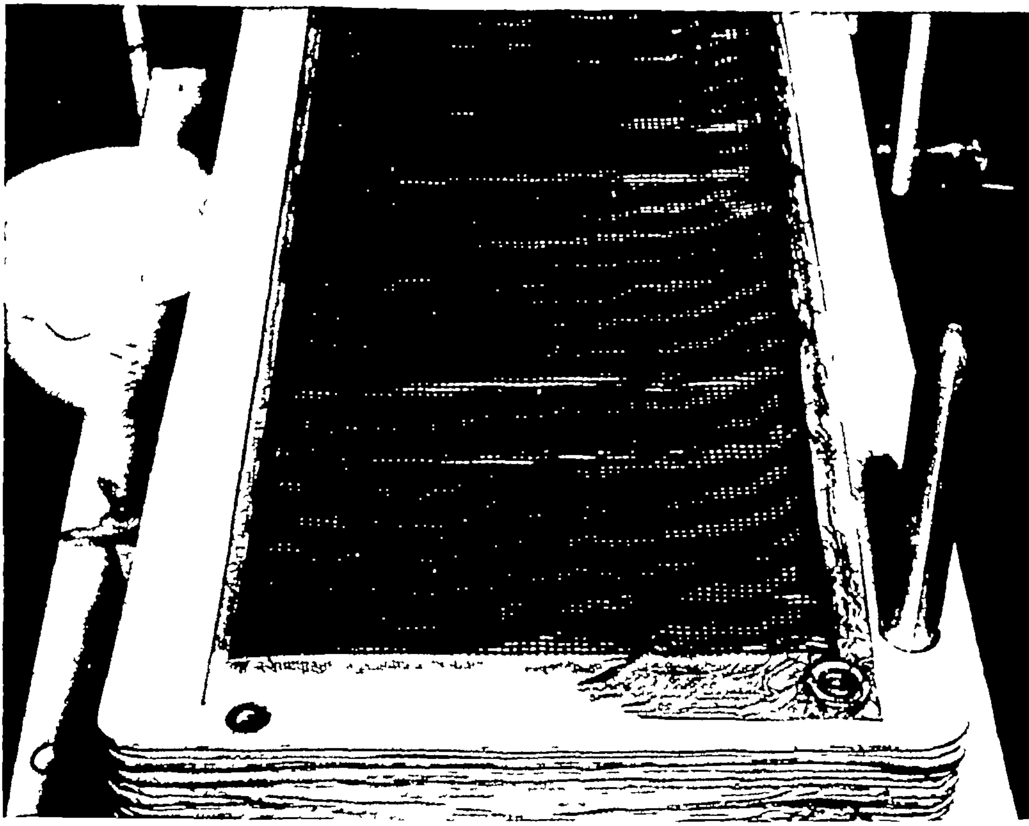


FIG 33 View from the end of the oxygenator being disassembled, showing a blood-filled membrane lying on one of the grooved supporting plates This shows the channels of blood flow down sides and across the surface At right is a blood distribution ring between the layers of membrane, marked "B" Beside this is an alignment post for accurate superposition of the mat At left, marked "O," is the oxygen distribution channel communicating with the grooves on top and the screens below each mat

a chlorine-releasing solution, to the assembled apparatus for two hours before use

Initially normal physiologic saline solution is recirculated through the apparatus to remove all trapped air bubbles which can be bled off from the bubble trap by stopcock "B" The saline is then drawn off and replaced by dextran which is in turn replaced with fresh heparinized whole blood Unless the whole apparatus is heated to 38° C or a blood heating coil is used at the outflow from the oxygenator, the blood will rapidly assume room temperature

Operation of the apparatus is quite simple The closed circuit is illustrated in Figure 34 Since the apparatus contains a constant

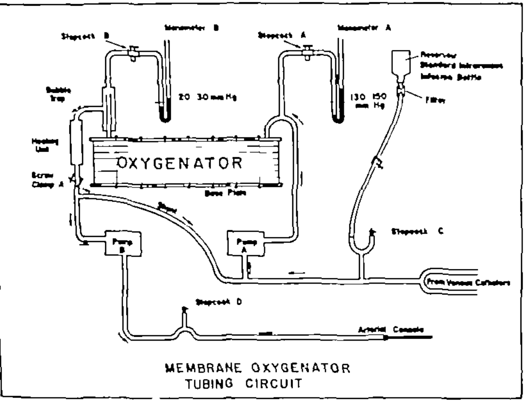


FIG 34 The diagram of blood flow through the closed circuit of the oxygenator Blood is continually recirculated and is only drawn through the venous connection when blood is pumped from the system into the arteries

volume of blood, one is assured that the quantity of blood pumped from the veins is simultaneously returned to the arteries The membranes stretch to different degrees with varying pressures Therefore it is necessary to have a constant pressure within the apparatus to maintain a constant volume This is accomplished by setting pump "A" at a fixed rate (about 50 cc /unit/minute) The inflow and outflow pressures are then checked by manometers "A" and "B" When the apparatus is fully primed the clamp is removed from the venous side Little blood will be drawn into the oxygenator until the arterial pump is started Perfusion then becomes entirely automatic Blood need only be added as it is lost from the subject being perfused. At the termination of the procedure the perfusion is stopped simply by shutting off the arterial pump and clamping the venous tube Recirculation is continued until such time as it is determined that the oxygenator will no longer be necessary

EXPERIMENTAL PROCEDURE AND RESULTS

Efficiency of Oxygenation: A series of experimental perfusions were performed to determine the volume of oxygen delivered to blood by the machine per minute and to determine the trapped volume of blood while in operation The rate of blood flow in the apparatus was measured by the rate of outflow from a reservoir with the shunt and venous tubes temporarily clamped Changes in volume at various flow rates could easily be measured during recirculation of blood through the shunt with all vascular connections clamped by observation of changes in the reservoir level Blood samples were removed for Van Slyke analysis from the arterial and venous lines To make certain that the oxygenator was giving maximum oxygen transmission to the blood the apparatus used was purposely set up with too small a surface area for the given animal so that it did not deliver fully saturated arterial blood

The effective transmission of gas through a given membrane area may be expressed by the formula (2), since each unit of the oxygenator contains very nearly one-half square meter of surface area

$$\frac{O_2 \text{ delivered (cc /min)}}{\text{Membrane area (sq M)}} = \frac{\text{A-V Diff (vols \%)} \times \dfrac{\text{flow rate (cc /min)}}{100}}{\dfrac{\text{Number of oxygenator units}}{2}} \qquad (2)$$

From the point of view of actual usefulness for clinical purposes, it is important to compare the amount of oxygen delivered per minute with the volume of blood contained in the apparatus during perfusion This is best expressed in terms of the number of 500 cc blood transfusion units required to fill the apparatus, and is given by the formula

$$\frac{O \text{ delivered (cc /min)}}{\text{Priming blood transfusion units}} = \frac{\text{A-V Diff (vols \%)} \times \dfrac{\text{flow rate}}{100}}{\dfrac{\text{Total Blood Volume}}{500}} \qquad (3)$$

TABLE II

EFFICIENCY OF MEMBRANE OXYGENATORS

	Flow Rate (cc /min /Sq M)	*A V Diff*	*Priming Vol of Oxygenator per Sq M Area (cc)*	*Oxygen Delivered per Sq.M Area (cc /min) (formula *)*	*Oxygen Delivered per 500 cc Priming Blood (cc /min) (formula 3)*
Oxygenator A Polyethylene 0 0008 in	200	2 7	110	5 4	10 2
Oxygenator B Polyethylene 0 0008 in	50	0 4	80	4 7	29 4
	100	6 8	100	0 8	34 0
	200	3 5	115	7 0	24 1
Oxygenator C† Teflon 0 0005 in.	200	10 0	150	21 8	83 5

* Described in a previous publication.[12] Oxygenators A and B each have a membrane area of 0.5 square meter per unit

† These results were calculated from data obtained using a small oxygenator constructed to test a sample of Teflon in oxygenating flowing blood

Data in Table II indicate that in Oxygenator "B" considerably greater efficiency of oxygenation was obtained compared with Oxygenator "A" by substitution of a screen mesh in place of the grooved support on one side of each pair of membranes Using 0.8 mil polyethylene a blood flow rate of at least 50 cc per minute through each unit is desirable to attain the greatest effective transmission of oxygen through the membrane At this level the inflow pressure reaches approximately 100 mm Hg which seems to be required to assure good blood distribution to all parts of the membrane Flow rates above 100 cc sq M /min. do not materially increase the oxygen diffusion and simply increase the volume of trapped blood by increasing the pressure

Polyethylene 0 8 mil in thickness has been found to transmit between 6.2 and 7 1 cc of oxygen per square meter per minute in actual operation of the apparatus This gives an efficiency varying from 76% to 86% of the theoretical maximum possible as shown in Table I

Surface Area and Perfusion Rate To determine the blood flow rate per minute and the volume of oxygen supply necessary to maintain physiologic conditions during total perfusion of the body with a membrane oxygenator four groups of experiments were

carried out. The animals were subjected to occlusion of the pulmonary artery or vena cavae for periods of one hour while circulation was sustained by the apparatus. In the first and second groups a surface area of membrane large enough to supply the theoretical amount of oxygen required by the animal under anesthesia (7.5 cc./kg.) was employed. The first group were perfused at a flow rate as high as convenient ranging from 74 to 93 cc./kg./min., the second from 27 to 41 cc./kg./min. For the third and fourth groups of nine and ten dogs respectively an oxygenator was set up which contained only one-half the calculated requirement for membrane area. Group III were perfused at a high flow rate ranging from 74 to 89 cc. per kg. per minute, while the fourth had low rates of 24 to 37 cc./kg./min. The rectal temperature of these animals was maintained throughout the procedures between 35°C and 37°C.

At intervals during these experiments, arterial oxygen, carbon dioxide, pH, and lactic acid levels were measured. The state of the animal was followed by means of the electroencephalogram, the electrocardiogram, and blood pressure recordings. Of the first groups, nine of ten animals survived. One died of a technical error and hemorrhage. Of the second group (adequate oxygenation with low flow rate), six of ten survived, but it was noticed that these animals were slower in recovering and showed some slight degree of brain wave depression during the procedure. Of the third and fourth groups (perfused with inadequate oxygenators) only one animal survived. By contrast with the first two groups all animals of these latter groups showed severe depression of the brain waves during the latter part of the long-long total perfusion. The deaths took place in a state resembling normovolemic shock in that they did not respond to replacement transfusion. It is of interest that in both groups inadequately supplied with oxygen the animals developed very low venous oxygen tensions and severe acidosis with CO_2 and lactic acid accumulation in the blood; pH level fell to 6.8 or lower. It appears that this severe acidosis was the chief cause of death in these animals. A summary of this data is given in Table III.

Survival of Prolonged Perfusion. A series of eight dogs were subjected to total perfusions for periods of two and one-half to

TABLE III

THE EFFECT OF ADEQUATE AND INADEQUATE OXYGENATION AT HIGH AND LOW FLOW RATES DURING TOTAL PERFUSIONS OF ONE HOUR

	Membrane Area (Sq M/kg)	Perfusion Rate (cc/min/kg)	Mean Arterial B P mm Hg	Arterial Blood End of Perfusion: O_2 Saturation	Arterial Blood End of Perfusion: Blood pH	Oxygen Consumption % of Control	Survival: Left	Survival: Number
Group I	1	81	97	90% ± 1.5	7.40 ± 0.3	88% ± 6	10	6
Group II	1	32	18	91% ± 0.7	7.42 ± 0.6	85% ± 8	10	6
Group III	0.5	81	38	37% ± 6.2	6.80 ± 1.2	49% ± 7	9	0
Group IV	0.5	30	11	70% ± 3.1	6.93 ± 0.9	13% ± 1	10	1

three hours using oxygenators of adequate area and high flow rates. The right atrium was opened in all of them for exploration with an electrocardiographic electrode.* Six of these recovered and survived for two days before sacrifice.

Hemolysis. Dog red blood cell fragility varies greatly from animal to animal. The average free hemoglobin in the plasma at the start of eleven one hour perfusions was 34 mgm % and at the end 62 mgm %. Platelet count during this period was reduced an average of 24% of the control level. With only one exception among this group the platelet count was greater than the control level two hours postoperatively. The white cell count varied greatly but was generally somewhat reduced at the end of perfusion with a marked rise above normal two hours postoperatively.

Clotting Mechanism. Heparin 1.5 to 2 mgm per kilogram of body weight was administered intravenously. Twenty four mgm of heparin per liter was placed in the donor blood which is nearly equivalent to that in the animal's circulating blood volume. At the termination of the procedure protamine sulfate in 5% glucose solution was given intravenously by slow drip in approximately the same doses as the initial intravenous heparin. Clotting time[18] usually returned to less than five minutes by the end of this infusion.

In the early use of the membrane oxygenators for complete perfusions it was observed that uncontrollable bleeding frequently occurred postoperatively despite the use of protamine and other precautions. This proved to be related to the degree of hemo-

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* Experiment performed in association with Louis Rakita, M.D. of the Department of Medicine, Cleveland City Hospital.

dilution that took place in filling the oxygenator with donor blood. If dextran were not almost entirely replaced with blood this phenomenon was apt to occur In general a hematocrit below 30% at the termination of the procedure has resulted in bleeding difficulties

Bleeding time was estimated one hour postoperatively in the majority of dogs in which survival from one hour perfusions was expected This was done by needle prick on the under side of the tongue as suggested by Kolff [10] In all but 15% of the animals which survived, this had returned to near control times by completion of the protamine infusion Clotting and bleeding times both remained elevated in 80% of the animals which were inadequately oxygenated

CLINICAL USE OF THE MEMBRANE OXYGENATOR

Nine elective perfusions were undertaken for cardiotomy to correct intracardiac disease All were seriously ill patients urgently requiring operation Two were babies under six months of age, and one was two years old These three died There were six adult women ranging from 49 to 65 kilograms in weight, of whom three are well Among the six patients who failed to survive, all but two made a complete recovery from anesthesia and died two or more days later of other complications Of the two who failed to recover fully from anesthesia one was a baby in whom an error in diagnosis prompted closure of an interatrial septal defect in the presence of total anomalous pulmonary venous drainage into the left subclavian vein The other was a woman who was reoperated upon for severe mitral regurgitation Massive scarring at the base of the heart made clamping of the aorta impractical Blood was regurgitated at such a rate that it became necessary to return the blood sucked from the atrium to the oxygenator A small amount of foam was introduced and found in the arterial line postoperatively This woman was semi-conscious postoperatively, but was otherwise doing well until eight hours later At that time she developed severe pulmonary edema Post-mortem disclosed that the sutures used to repair the valve had cut through the tissue

Data from these perfusions is summarized in Table IV An

TABLE IV

DATA FROM CLINICAL PERFUSIONS*

	Adults[a]		Children[b]	
	Average	*Range*	*Average*	*Range*
Perfusion Time (Minutes)	28	(25 37)	24	(10–31)
Complete Bypass Time	21	11–20)	18	(12–23)
Flow Rate (Liters min)	2 4	(1 3 2 9)	0 8	(0 6 1 1)
Blood Pressure Mean (mm Hg)	02	(2–105)	08	(58 82)
Oxygen Uptake (cc min)	100	(1 3 182)	38	(33–42)
Arterial Blood End of Perfusion				
Oxygen (Saturation)	01%	(81 0)	02%	(88–04)
pCO_2 (mm. Hg)	42	(32 53)	30	(30–43)
Lactic Acid (mgm %)	40	(30–71)	33	(20 30)
pH	7 31	(7 21–7 34)	7 34	(7 31–7 36)
Free Hgb (mgm %)	51	(33–125)	61	(— —)
Platelet Depression	17%	(4 5 24)	22%	(14–32)

oxygenator of adequate surface area to meet the oxygen requirements of the patient was used With but one exception fully oxygenated blood was perfused into the arterial system of each patient. Flow rates in the adults ranged from 38 to 52 cc /kg /min while those in the children were from 72 to 91 cc /kg /min Arterial blood pH remained near the control levels in every case Normal clotting was restored to every patient without difficulty by the use of protamine titration and the infusion of one or two freshly drawn blood transfusions as the operation was being completed

Two patients with cardiac arrest who could not be resuscitated by the usual methods were connected to the apparatus as an emergency Ordinary bank cross matched blood which was heparinized was used to prime the oxygenator The citrate was then neutralized with calcium chloride solution (1 gram per 500 cc) Although the heart of the first patient could not be restarted due to a coronary occlusion he regained consciousness while being perfused The other patient s heart which was initially damaged by a massive venous air embolism was eventually made to beat effectively She became hypertensive but did not recover consciousness and died four days later In the first case the heart was massaged for two hours before the apparatus could be assembled and connected to the circulation In the second about thirty minutes elapsed since the oxygenator happened to be set up

These two perfusions were run for approximately one hour at flow rates of 52 cc /kg /min (3400 cc /min) and 45 cc /kg /min (2600 cc /min) Oxygen saturation was above 90% in each However, the arterial blood pH which was below 7 1 and 7 06 respectively at the outset of these perfusions remained low throughout although pCO_2 fell to 32 and 35 mm Hg Free plasma hemoglobin rose 42 mgm % in one and 29 mgm % in the other during the hour of artificial maintenance of circulation

DISCUSSION

Two virtues are apparent in the use of the membrane oxygenator First it is an entirely closed system not subject to the dangers of entraining gas bubbles to be pumped into the arterial system of the organism being perfused Secondly it is apparently free from the production of particulate emboli over periods up to three hours In the absence of leaks it is not subject to changes in volume as long as flow and pressure are kept constant If these were not true, it is doubtful that total perfusions for periods of up to three hours could be accomplished with survival

The limiting factor in the effectiveness of a membrane oxygenator is the volume of oxygen and carbon dioxide which can be transferred through a given area of a given membrane per minute It was amply demonstrated by the lack of survival of Groups III and IV in Table III that the surface area of membrane used must be adequate to transfer as much oxygen per minute as an animal or patient will use Otherwise, oxygen saturation of the arterial blood falls off and acidosis results Therefore, the problem exists as to how best to obtain a large enough surface area without having the apparatus hold an unreasonable amount of blood

There are two approaches to this problem The first is to use available membrane with the greatest oxygen diffusing capacity The second is to produce the thinnest possible film of blood flowing between the membranes with a minimum volume wasted in distribution The former problem was settled by diffusion tests showing that polyethylene 0 0008 inch in thickness was the most suitable of the plastic films then commercially available Recently at the suggestion of Clark,[14] Teflon film 0 0005 inch in thickness was obtained and tested This proved capable of diffusing approxi-

mately 3.5 times as much oxygen for a given area in one minute to venous blood as was polyethylene 0.0008 inch. It has proven in small models to be similarly effective in oxygenating flowing blood. Judging by the data presented in Table II it is possible that an adult man requiring more than 200 cc. of oxygen per minute might well be oxygenated with an apparatus containing only 1200 cc. of blood. This is in contrast to the present use of polyethylene which at best requires more than 3000 cc. for such a purpose. It must be remembered, however, that for smaller patients or animals a smaller surface area may be set up proportional to the organism's oxygen requirement. This means that there will be an amount of blood trapped in the apparatus again proportional to the oxygen requirements.

Data in Table II make it clear that the most efficient use of both the membrane surface area and the volume of blood being pumped between the membranes has been attained by the Oxygenator "B" described in this paper. It is based upon earlier observations on flow and resistance which indicated that a short effective exposure of blood to the membrane requires less volume and pressure than is required if blood is pumped through a long distance with a small cross section. The design is now so arranged that blood is distributed along the long side of the oxygenating surface and made to flow in channels across its short dimension.

Data on hemolysis suggest that with the Sigmamotor pumps used in these experiments and clinical operations the damage to red cells is comparable with other types of oxygenators.[2,4,14] Kolff[9] in the use of the coil type of membrane oxygenator obtained data showing blood cell and platelet destruction of essentially the same order. In other words, exposure of flowing blood to large surfaces of polyethylene for long periods does not result in serious blood damage. It is true that membranes become coated and wettable but apparently do not trap or destroy dangerously large numbers of platelets or white cells. Difficulty has not been experienced with the clotting mechanism provided that adequate oxygenation of the animal was maintained and that severe hemodilution did not take place in priming the apparatus.

Certain disadvantages have become apparent in this type apparatus. In the earlier stages it was difficult and time consum

ing to assemble Recent improvements in design have made it possible to set up the equipment for perfusion of an adult patient in a period of about two hours

Sterilization has been dependent upon the use of cold sterilizing fluids, yet no blood culture following a clinical operation has grown organisms This is in part due to the fact that all parts which come into contact with blood including the membranes and tubes are disposable

Leaks have been the greatest hazard If they occur, dangerously large volumes of blood may be lost in the course of a relatively short time Yet careful examination of the membranes for flaws and attention to details of assembly have resulted in only one leak of serious proportions, in the clinical series All of the long perfusions performed in animals were accomplished with leak-proof assemblies The proposed use of Teflon may further eliminate this hazard, for in the short series of experiments conducted to date no instance of leakage has yet occurred

SUMMARY

An efficient blood oxygenator dependent upon the diffusion of oxygen and carbon dioxide through thin plastic membranes is described It is capable of attaining an oxygen transmission rate up to 85% of the maximum expected for a given membrane

Of the plastic membranes tested polytetrafluorethylene (Teflon) 0 5 mil in thickness has proven the best, being capable of transmitting 24 cc of oxygen per minute to blood In operation it has been demonstrated to pass 21 8 cc of oxygen per minute to flowing blood Polyethylene 0 8 mil in thickness was used for most of the experimental work and is only about 30% as effective as Teflon A variety of other membranes have proven unsuitable

The efficient use of blood to avoid trapping large volumes in a membrane oxygenator depends upon the exposure of a thinly flowing blood film to the greatest possible area of the membrane surface within the apparatus This is accomplished by reducing resistance and pressure to a minimum by a short passage of blood as it travels across the membrane This is accomplished by pumping blood between two layers of membrane at a rate and pressure adequate to distend the membranes into grooved surfaces sup-

porting it on the outside to form channels in which the blood can flow

A multiple unit oxygenator having up to 30 square meters of surface area has been designed and constructed which is capable of completely supporting the circulation and respiratory needs of animals for as long as three hours It has been used also successfully for operations on adult man The number of the units of the apparatus to be used for a given perfusion is dependent upon the surface area of membrane needed to pass the amount of oxygen required per minute by the animal or patient

The authors wish to express their appreciation to Mr L. W Sahley of the Cleveland Scientific Equipment Company for his keen interest and help in engineering Through his kindness the latest model of the oxygenator was built Also the faithful assistance of Mr Howard Peacock of our staff has made possible much of the work reported

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DISCUSSIONS ON OXYGENATORS

DR. EARLE B KAY Cleveland I am indebted to Dr Gross who brought a slide of one of his oxygenators The principle we have used in the rotating disk oxygenator is one developed by Dr Bjork which consists of a cylinder of glass We have used a larger priming volume of 1400 cc., 800 of which is necessary and 600 of which is used as a reservoir We can get a perfusion rate of from 2,000 to 6 000 cc. per minute depending on the size of the oxygenator and the size of the individual. We have had as high as 103% O_2 saturation and a CO_2 tension of between 30 and 40 mm Hg Using the oxygenator for perfusion there has been an imperceptible increase in hemolysis From our viewpoint it has been a perfectly satisfactory apparatus We have now done 104 patients with this type of apparatus There has been an over all mortality of 34% There has been only one mortality in the tetralogy and this patient had been operated upon twice The apparatus using a Sigmamotor pump is regulated by venous manometers which control the pump during the course of the procedure

WILLEM J KOLFF Cleveland In the three minutes allotted I want to make three practical points

1) THE PROBLEM OF OVER-OXYGENATION We have reason to believe that over oxygenation may be responsible for some unexplained complications and deaths that have occurred in the past Whether or not this is so cannot be proved A good way to avoid over oxygenation with any type of oxygenator is by the use of a Clark Polarograph* which is now commercially available † In Figure 35A and B the Clark Polarograph electrode is shown together with the equipment that provides a 2 microampere current with 6 volts through the electrode A galvanometer reading corresponds to a certain oxygen tension. Figure 36 shows how we use this polarograph to maintain adequate oxygenation during the bypass but mainly to avoid over-oxygenation At the beginning of the graph the reading on the galvanometer is low corresponding with the oxygen tension of the venous blood then present in the oxygenator When oxygenation is started with air equilibrium takes place after a certain time and we assume that this represents from 95% to 98% saturation When the pump is started and venous

*Monitor and Control of Blood and Tissue Oxygen Tensions by Leland C. Clark, Jr., *Transactions* American Society for Artificial Internal Organs Vol. II pp 41 1956

† Yellow Springs Instrument Company Yellow Springs, Ohio

8 Inouye, W Y Construction and performance of our dialyzer *Tr Am Soc Art Int Organs, 1* 36, 1955
9 Kolff, W J and Balzer, R R Artificial coil lung *Tr Am Soc Art Int Organs, 1* 39, 1955
10 Kolff, W J , Effler, D B , Groves, L K , Peereboom, G , and Moraca, P P Disposable membrane oxygenator (heart-lung machine) and its use in experimental surgery *Cleveland Clin Quart , 23* 69, 1956
11 Clowes, G H A , Jr , Hopkins, A L , and Kolobow, T Oxygen diffusion through plastic films *Tr Am Soc Art Int Organs, 1* 23, 1955
12 Clowes, G H A , Jr , Hopkins, A L , and Neville, W E An artificial lung dependent upon diffusion of oxygen and carbon dioxide through plastic membranes *J Thoracic Surg , 32* 630, 1956
13 Clowes, G H A , Jr , and Neville, W E Further development of the membrane oxygenator *Tr Am Soc Art Int Organs, 3* 1956 (In press)
14 Clark, Leland Yellow Springs, Ohio Personal Communication
15 Wintrobe, M M *Clinical Hematology,* Philadelphia, Lea, 1946
16 Kay, E B , Zimmerman, H A , Berne, R M , Hirose, Y , Jones, R D , and Cross, F S Certain clinical aspects of the use of a pump oxygenator *J A M A , 162* 639, 1956

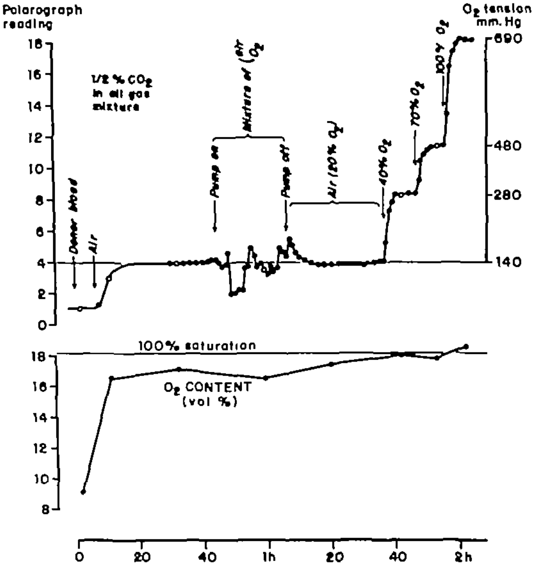


FIG. 36 Shows the recorded readings on Clark polarograph during its use in a by pass procedure (Dr Kolff)

blood of the patient starts to come into the oxygenator there is a fall of oxygen tension which is compensated by adding more oxygen to the gas mixture in the oxygenator and by eliminating the air completely if necessary Thus the same oxygen tension is maintained during the bypass After the bypass while the blood remains in the oxygenator we revert to air to avoid over-oxygenation of the blood in case it is later needed.

For the sake of an experiment, increased percentage of oxygen was later added to the gas mixture while the blood was being circulated It can be seen that the oxygen tension as indicated by the galvanometer

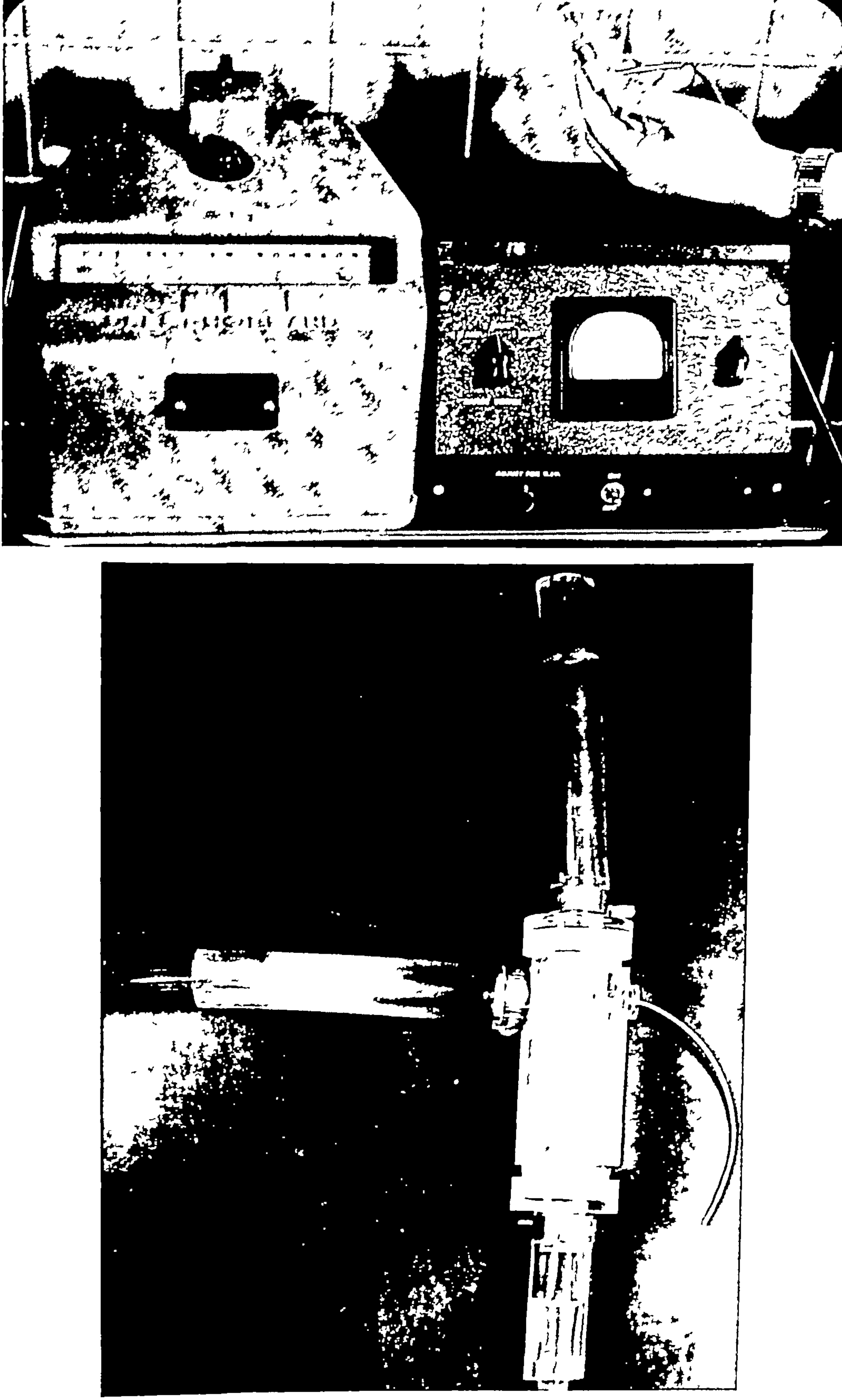


FIG 35 A AND B Clark polarograph and electrode (Dr Kolff)

to leave the downward curvature of this plastic tubing and it forms the most reliable bubble trap we know

In summary 1) We recommend the addition of a Clark polarograph on the arterial end of the oxygenator 2) Tanks with undiluted CO_2 should be avoided 3) An effective filter—bubble trap is described

DR. F JOHN LEWIS Chicago In this discussion I thought I could at least define my experience in membrane oxygenation because it is quite unsuccessful We used polyethylene in our oxygenator 24 inches wide, which cost $24.50 We used it for months and finally gave it up When we became interested in membrane oxygenators we were acquainted with Clowes work but I could not understand how blood could go through George Clowes machine So we designed our own Its main feature is that the membrane is cut up into sections and the bag is sewed into the tube of polyethylene The blood goes down and through capillary movement reaches the patient in rivulets You can tell immediately whether you are getting good distribution or whether there are any leaks developing by visual control This remarkable oxygenator has a capacity of 12 units Our objective has been to use 1200 cc per minute If the venous saturation is around 80% we can get 90% saturation at outflow Many of our total perfusions are of 30 minutes duration so our arterial oxygen saturation falls to a level of 85%

The blood is kept at the lower end of the reservoir This unit holds about 500-700 cc. For our total by pass experiments we use 2 units of blood, and the apparatus eliminates any danger of antifoam emboli I am not sure if the danger of fibrin emboli is any less The difficulty has been in obtaining adequate oxygenation As an aid we put the en tire apparatus in a big box and increase the pressure to 200 mm Hg Temperatures in the box above 35°C seem to improve oxygenation

DR JOHN J OSBORN San Francisco I have prepared a paper on surface tension which I am not going to use There are some points which came up which seem to be more interesting than my prepared paper

The first thing that strikes me in the design of oxygenators is that like the design of airplanes everything you do is a sort of compromise We have heard from one end to the other of different kinds of com promises today One of the most important things one has to compromise on is simplicity The first car my father used had a very simple carburetor which never worked The carburetor of my modern car is very complicated but works without trouble We want simplicity for

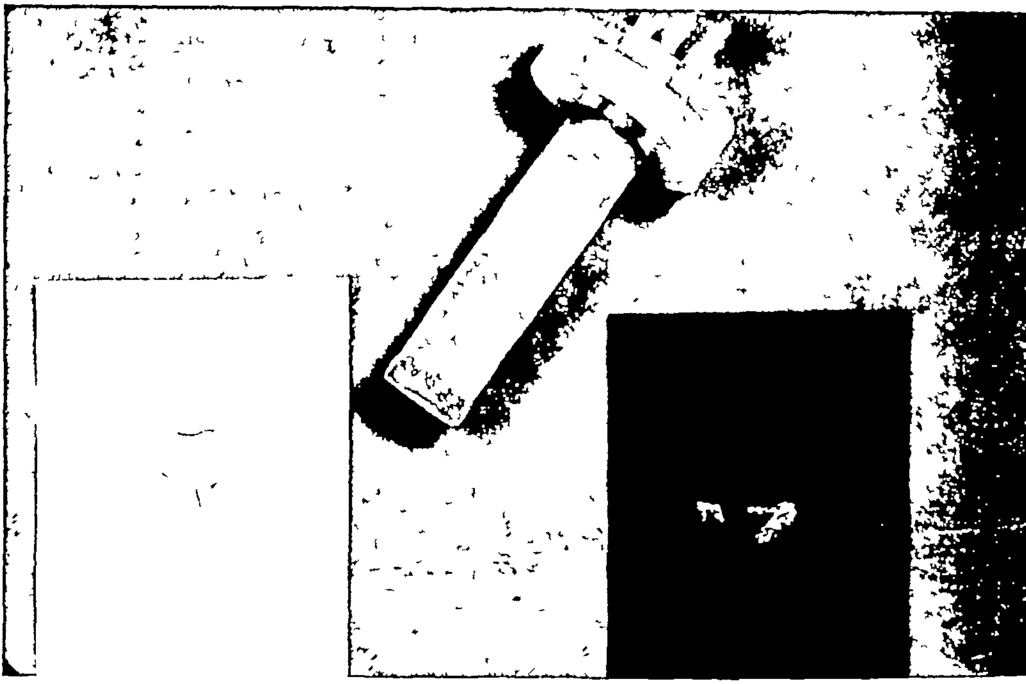


FIG 37 Silk threads aspirated from operative field and Teflon shavings from the oxygenator, both of which entered extracorporeal circulation during use, a filter for blood in the circuit is necessary to safety (Dr Kolff)

increases to very high levels, 690 mm Hg The lower line in the graph indicates the conventional way of determining oxygen in blood in volumes percent It is very difficult to detect over-oxygenation in this way as only a few volumes percent of oxygen physically dissolved in the blood are responsible for the extreme increase in oxygen tension

2) *TANKS WITH UNDILUTED CO_2 SHOULD BE AVOIDED* If one wants to add CO_2 to the gas mixture in any type of oxygenator to avoid excessive removal of CO_2 from the blood, the CO_2 should not be added from a tank with undiluted CO_2 If the gauge is off, which according to our experience it may well be, intoxication with CO_2 may result However, any desirable concentrations of CO_2 may be arrived at by mixing pure oxygen with oxygen containing 3% CO_2 In this way it is impossible to get a higher concentration than 3% of CO_2 in the final mixture even if the gauge is faulty

3) *ONE MUST HAVE A FILTER IN THE ARTERIAL OUTFLOW LINE* A 50 gauge stainless steel filter is shown in Figure 37 Silk threads were retrieved from the filter They had been sucked up in the open heart Teflon shavings were derived from a commercially available oxygenator We have put this filter between slowly curved polyvinyl tubings of 1" I D In Figure 37 this tubing is not bent downwards such as it is during actual use Even very small bubbles are reluctant

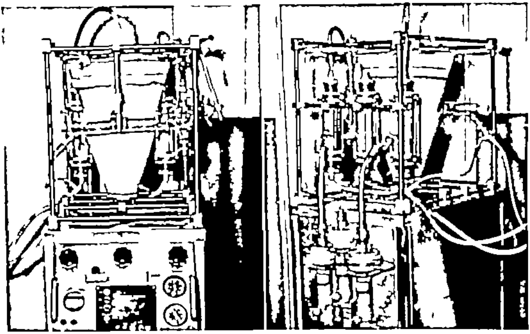


FIG 38 A AND B Anterior and lateral view of the pump-oxygenator used by Salisbury

useful in the treatment of acute heart failure We have designed and tested a disposable heart lung machine with automatic safety features which has a blood capacity of 350 cc (in the adult this low priming volume would permit the use of plasma as a priming fluid) and which can safely pump and arterialize 1 500 cc per minute (Fig 38A & B)

Both our surgical and our new "medical" heart lung machines arterialize blood with the DeWall principle a continuously renewed cushion of blood-oxygen foam is used as the filming agent for the venous blood. The gentle bubbling of large gas bubbles is not traumatic and is well tolerated by the blood In this connection it must be said that the criticism which is so often leveled against the "foam" type of gas exchange equipment is hard to understand. Notwithstanding the merits of many membrane film type machines (they also have serious limitations and disadvantages which are not so often publicized) there has never been any evidence whatsoever which would prove acceptably the toxicity of "foam" type gas exchangers The physical principle which must be used in the separation of gas and blood is well known As we demonstrated in 1954 60 cm of horizontal transit of a shallow layer of blood will effectively eliminate even the smallest bubbles The great variability in the performance of the DeWall machine cannot indict the foam principle Firstly this machine has been used with outstanding success in many centers and secondly disappointing per

the operator but we do not necessarily need simplicity in the design Another consideration is how much hemolysis we will tolerate We do not want hemolysis, it is an indication of trouble If the red cells hemolyze this may be evidence that some other molecules in the system may be also damaged, yet extreme attention to hemolysis may require serious complexities in assembly

A third thing to consider is inherent safety due to design One example of this is Dr Poth's pump which he described earlier

The last thing which strikes me as important in thinking of the various compromises one has to make is disposability I think disposability is important When you can get something clean and sterile ready to use and then can throw it away afterwards, that is important You have to make a lot of compromises if you want to get disposability Yet I think it is one of the most important considerations in design I think it is interesting to consider these previous papers in terms of what compromises were made and what considerations were stressed most in working out the chosen design

DR PETER F SALISBURY, Los Angeles, California It is a real pleasure to take part in a meeting on perfusion where so many of the pioneers are present The many new faces are evidence of the tremendous interest in perfusion and attest the status attained by this group of procedures Judging from the program, the many speakers and discussants are expected to describe their particular type of equipment

The heart-lung machine, which has been developed here for surgical purposes (*J Appl Physiol*, 9 487, 1956), can pump and arterialize 5,000 cc blood per minute, has a priming volume of 1,500 cc, is completely free of bubbles and clots, does not cause detectable hemolysis in many dogs and humans when running as long as 60 minutes with complete by-pass when there is no excess suction in the coronary return system It does not seem to destroy an appreciable number of platelets, can maintain and control the blood pH by gas flow alone, is fully heat sterilizable, takes about 2 hours to set up and service for each run (including cleaning afterwards), has fully automatic level and volume controls, and has been successfully used in patients The automatic control features and the construction of durable, Teflon- or silicone-coated materials makes it somewhat more costly than other similar equipment, but it is felt that this is no prohibitive disadvantage

The use of heart-lung machines in open-heart surgery is now well established, but assisted circulation as a treatment in non-surgical heart disease is only in its infancy A machine which needs no priming blood and which is therefore operating at all times, would obviously be very

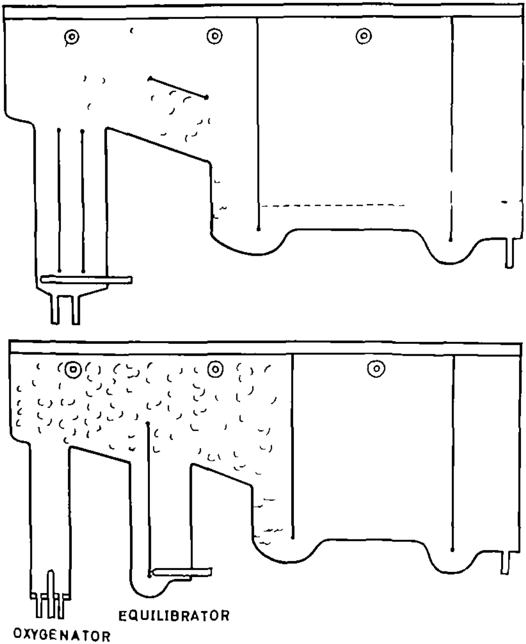


FIG 40A AND B Diagram of oxygenator (A) and of oxygenator with equilibrator added (B) (Dr Rygg)

type has only been used in the lab The different sections of the bags are not going to be discussed here More interesting is to deal with some of the observations related to the problem whether it is possible to eliminate the danger of air embolism in connection with bubble oxygenation of blood This is a matter of ridding the blood of the minute air bubbles which commonly may be formed in certain po-

formance and the appearance of bubbles may be due to the modification of the original apparatus

DR I H RYGG, Copenhagen During the past 1½ year tests have been made at Rigshospitalet of new and improved disposable plastic bag oxygenators for use in a heart-lung machine Working with other types of oxygenators it appeared desirable to make a disposable oxygenator including all the different parts necessary as one single unit, sterilized and ready for use

Bubble diffusion seemed to be the most suitable principle for this

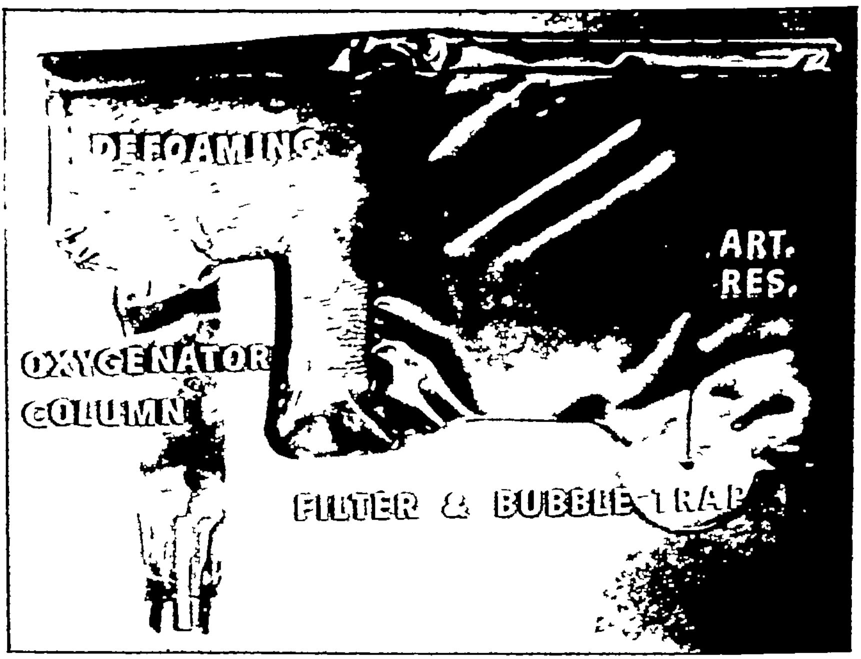


FIG 39 Plastic bag for oxygenator as used by Rygg, see also Figs 17 and 18

purpose, and a disposable unit was made by heat-sealing two layers of thin plastic sheet forming a sort of a bag providing consecutive sections for arterialization, defoaming filtration and storage of blood

Fig 39 shows a type of the plastic bag oxygenator which is used for flow rates up to 1 5 liter per min It is equipped with polyamide fibers imbedded with a thin layer of silicone antifoam (Dow Corning antifoam A) for defoaming and filtration of the blood and with inlets and outlets for blood and gases Fig 40A is a diagram of the type which is used for blood flows up to 4½ liter per min and Fig 40B is a type with an additional section called an equilibrator through which nitrogen, carbon dioxide and gases for anesthesia may be supplied This last

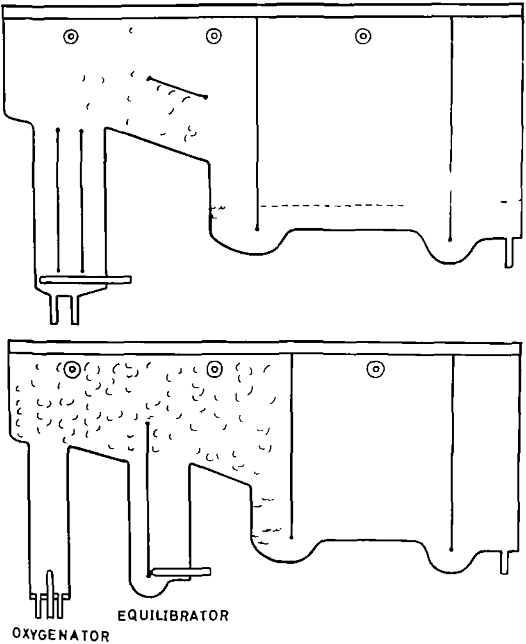


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DR EDWARD S HYMAN New Orleans La Several years ago we undertook the making of an oxygenator Although it was easy to aerate blood by bubbling it was soon apparent to us that what was needed was a mechanical device containing as a sterile preassembled and disposable plastic unit that portion of the device that was in direct contact with blood which could be mass produced while using the mechanical apparatus over and over again Sheet vinyl plastic offered a great versatility for the design of a unit that could be autoclaved After constructing several bubblers and filmers a unit was tested successfully on dogs It is a single unit including tubing which hangs from a metal rod It is stored sterile in a small package ready for use in a few minutes

I believe that the original maintains a distinct advantage in efficiency over the Travenol (Baxter) modification by virtue of its oxygen dispersion system and the placement of the filter The oxygen is slowly and evenly distributed by a long tube with many pinholes Oxygen flow is regulated so that the color change in the blood is complete by the time it reaches the end of the tube This results in an oxygen flow rate which is much less than is commonly used and allows some control of pO_2 There is a broad filter up in the reservoir where the linear flow rate is slow It is effective in removing not only solid emboli but also bubbles should they be present

We have gone on to modify this original design and now have arrived at a unit that allows a flow of eight or nine times its retained volume per minute with freedom from bubbles One can test a dog using only a little saline to prime this unit. Its design should result in greater safety when it is enlarged to require priming by blood

It is interesting that we too made a pump of sheet plastic similar to that of Dr Poth using flutter valves which can be integrated into the oxygenator unit

DR. DWIGHT E HARKEN Boston One uses 2000 cc of blood (dog or human not stated) and time and rate of flow are variable The next man uses fresh human blood at 500 cc a minute for 15 minutes another 1500 cc. of outdated human blood at 3000 cc a minute over and over again in his pump Hemolysis of course cannot be translated from one clinic to another in such terms The fragility of blood varies from animal to animal, human to human and day to day All of these factors are altered by volume rate and duration of flow through the pump Furthermore we need to know whether an oxygenator animal or patient was in the circuit

sitions 1 in the oxygenator, 2 in the defoaming where greater bubbles break, 3 where blood is allowed to fall with too great a velocity against an underlying surface and 4 where blood is sucked into a pump with a short and forcible filling period

Accordingly a simple defoaming at the top of a bubble oxygenator is not sufficient for ridding the blood of air bubbles An additional procedure is necessary after which there must be no possibility of new bubbles to be formed later on in the system

A small quantity of minute bubbles is almost impossible to demonstrate in whole blood experiments Therefore human plasma has been used in which the bubbles may be seen directly The bubbles are demonstrated by making some folds in the plastic sheet at the arterial reservoir of the bag Under certain conditions bubbles are gathered in some of the folds at certain places and can be seen directly or by means of a magnifying glass

As the result from these experiments it could be observed that

1 Without any additional procedure every designed bubble oxygenator examined had a critical plasma flow rate above which minute bubbles could be demonstrated This flow (1 to 1½ litre/min) was related to the velocity of the plasma and, but to a lesser degree, to the gas flow rate

2 The passage of the blood through a filter made of silicone-coated polyamide fibers was found to be sufficient for ridding the plasma of these minute bubbles even at flows up to 6 liters/min

3 Another observation not connected to bubbles, which, however, may be of even more importance with regard to the problem of embolism was found By application of silicone directly at the inner side of the defoaming sections of the bags small dots and drops could be observed in the plasma at flow rates between 2 and 3 liters/min This was also the result, when silicone was smeared directly on the polyamide fibers Gross examination of the defoaming products revealed that these particles were silicone These observations were usually related to the way in which this material was applied and after the fibers have been siliconized by means of a thin solution of silicone in ether in which they are dipped and no other siliconizing is used, particles have not been observed

However, this is a point of importance, and if particular attention has not been given to the application of silicone, this may have resulted in some deaths previously considered to be caused by air embolism, although we have no direct proof of death from silicone

oxygenator at the rate of 4 liters per minute results in no drop in platelet count no alteration of fibrinogen content only a few flecks of fibrin separate out on the nylon mesh and the plasma hemoglobin increases 5 to 10 mgm%

Figure 41 shows a double decked operating room This arrangement allows gravity flow from the patient directly into the oxygenator which is placed under the operating table The operating table is supported at its four corners and not at the center The lower deck need be only sufficiently high to allow headroom

The oxygenator chamber is a thin walled Tygon (S-22 1) tube such as is used to fabricate blood storage containers This tube is filled with nylon mesh (30 ft × 6 ft) The mesh protrudes from the end of the plastic tube to dip into the blood reservoir below and functions as a "wick" to afford a smooth flow of blood without splashing and bubble formation. The theoretical surface is about 350 000 square centimeters

At a flow rate of 1 liter/min the oxygenator entraps about 300 c c. of blood and at a flow rate of 4 liters/min approximately 800 c c of blood is entrapped. Transit through the oxygenator occurs in approximately 10 seconds The blood and humidified gaseous mixture (95% O_2 and 5% CO_2) enter at the top of the sealed chamber The lower end of the chamber is open and does not dip into the blood in the reservoir

DR FREDERICK S CROSS Cleveland Although we have been very satisfied with the function of the oxygenator described as the Gross Dennis and Kay we have been making modifications which we think will improve the functioning of the oxygenator Obviously oxygenation could be carried out to indefinite amounts by increasing the length of the cylinder and the number of discs There is a difference in flow which has been a minor one to date We plan to standardize further the oxygenator in parallel discs or in the number of discs This maintains a critical distance at the periphery The discs rotate against each other in this manner In the early experiments the revolutions used were around 120 per minute which we felt to be the upper critical level. By increasing the present disc level to higher speed we make the peripheral speed of the disc the same as the draining disc, and we will be able to get more oxygenation In addition this will overcome the slight degree of churning we get at the periphery Finally there is some turbulence where the blood enters Obviously with the blood entering in jets the amount of turbulence will be increased Dr Syrack at Columbia has made a larger base disc which is of help in this respect We feel that by pursuing these modifications some of these problems will be lessened

DR EDGAR J POTH, University of Texas Medical Branch, Galveston, Texas I should like to present another type of oxygenator which might be called a "smear oxygenator" The blood-gas interface is obtained by spreading blood mechanically onto a surface in an atmosphere of O_2-CO_2

The exchange chamber is a thin-walled Tygon tube filled with a rolled nylon mesh material which can be autoclaved and is disposable Ninety-five per cent saturation is obtained with a flow rate of 4 liters per minute of blood and 10 liters per minute passage of 95% O_2-5% CO_2 through this exchange chamber

There are no bubbles formed Preliminary priming or flooding of the chamber is required Ten passages of 10 liters of blood through the

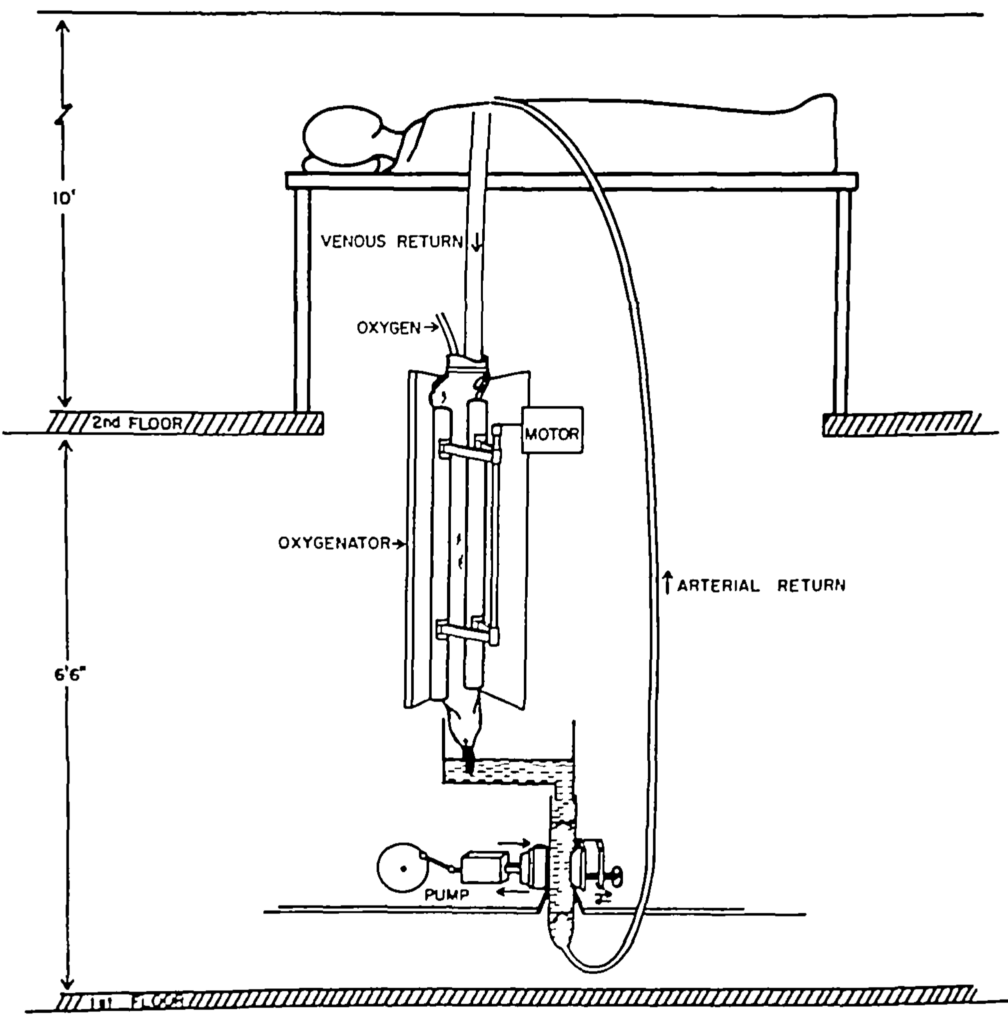


FIG 11 Diagram of gravity flow plastic bag oxygenator of Poth Note its two-floor extension

DR SAMUEL KAPLAN Cincinnati About eight years ago Dr Leland C Clark of our group originally described the method of coalescence of excess gas in blood by the use of antifoam (polymethyl siloxane) This method is an essential part of all bubble oxygenators and I am pleased that it has been accepted universally In our bubble oxygenator oxygenation occurs in a chamber having a pressure of about 100 mms Hg below atmospheric pressure and is accomplished by the exposure of venous blood to small oxygen bubbles (± 20 microns) Although the large surface area produced by small bubbles is excellent for oxygenation of blood the simultaneous use of larger bubbles (± 200 microns) insures the removal of adequate amounts of carbon dioxide We have monitored our human and animal perfusions by the continuous recording of the oxygen tension (measured polarographically) and pH of the arterial blood We are able to control the arterial pO_2 to within 10 mms Hg and the pH to four one hundredth of a unit In our small series of eleven human perfusions a pulsatile pump returned arterial blood which had a tension of between 400 and 500 mms Hg We have not noted any deleterious effects produced by perfusion of humans or dogs with arterial blood having a high oxygen tension We believe that a pulsatile arterial return is not dangerous and may indeed be beneficial particularly in a state of low flow rate which may on occasion be inadvertently encountered.

DR ROBERT S SHAW Boston I believe that the bubble oxygenator does produce a "beat up" blood a little more than the other oxygenator but this is the poor man s oxygenator and we intend to make the most of it We have tried to find out what causes hemolysis in the bubbling oxygenator In the first place hemolysis takes place at a rate which is constant with time It is not a problem unless the procedure goes beyond one hour The objective is to make perfusion possible for a long time Hemolysis or rate of hemolysis is also linear with the rate of bubbling After thinking about this air delivery which Dr Clowes brought out we compared the rate of hemolysis using warm saturated oxygen with its rate using dry oxygen we found about 40% reduction in the rate of hemolysis using warm "wet-oxygen"

We also wondered about toxicity of 100% oxygen and live red cells We know it is toxic to those cells under long exposure but there was no bubbling up to one hour when we used warm oxygenated air

DR HUGH F FITZPATRICK New York I would like to make a very simple but practical suggestion for those who are working with the Sigmamotor pump It is well known at the University of Minnesota,

DR HENRY T BAHNSON, Baltimore We have been interested in the possibility of pyrogens causing difficulty with perfusions Pyrogens cannot be easily demonstrated, the most sensitive test being injection into a rabbit with subsequent observation of temperature Material circulated through the pump could be pyrogenic at times Although bacteria are among the common types of pyrogens we could not usually grow bacteria and knew of no way the apparatus became contaminated Mr J F Edwards, an engineer in our team, suggested staining the material lining the tubing at the end of a "run", he found 1 per cent toluidine blue would stain material on the screens and other parts I would emphasize that this material was present after an extraordinarily thorough cleansing of all equipment with scrub bushes and various detergents We were not sure of the significance of these deposits but were happy to learn that soaking in 20 per cent sodium hydroxide for an hour removed it without damaging lucite or steel parts We boil the steel parts for good measure (see Figure 42)



FIG 42 Protein coagulum appearing as rough surface, remaining in tubes of extracorporeal circulation after use despite "thorough cleansing," suggests this is a source of pyrogens in the use of pump oxygenators and emphasizes the need for disposable 'single-use' units (Dr Bahnson)

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FIG 42 Protein coagulum appearing as rough surface, remaining in tubes of extracorporeal circulation after use despite 'thorough cleansing,' suggests this is a source of pyrogens in the use of pump oxygenators and emphasizes the need for disposable single-use units (Dr Bahnson)

DR SAMUEL KAPLAN Cincinnati About eight years ago Dr Leland C Clark of our group originally described the method of coalescence of excess gas in blood by the use of antifoam (polymethyl siloxane) This method is an essential part of all bubble oxygenators and I am pleased that it has been accepted universally In our bubble oxygenator oxygenation occurs in a chamber having a pressure of about 100 mms Hg below atmospheric pressure and is accomplished by the exposure of venous blood to small oxygen bubbles (± 20 microns) Although the large surface area produced by small bubbles is excellent for oxygenation of blood the simultaneous use of larger bubbles (± 200 microns) insures the removal of adequate amounts of carbon dioxide We have monitored our human and animal perfusions by the continuous recording of the oxygen tension (measured polarographically) and pH of the arterial blood We are able to control the arterial pO_2 to within 10 mms Hg and the pH to four one-hundredth of a unit In our small series of eleven human perfusions a pulsatile pump returned arterial blood which had a tension of between 400 and 560 mms Hg We have not noted any deleterious effects produced by perfusion of humans or dogs with arterial blood having a high oxygen tension. We believe that a pulsatile arterial return is not dangerous and may indeed be beneficial, particularly in a state of low flow rate which may on occasion be inadvertently encountered

DR. ROBERT S SHAW Boston I believe that the bubble oxygenator does produce a "beat up" blood a little more than the other oxygenator but this is the poor man's oxygenator and we intend to make the most of it We have tried to find out what causes hemolysis in the bubbling oxygenator In the first place hemolysis takes place at a rate which is constant with time It is not a problem unless the procedure goes beyond one hour The objective is to make perfusion possible for a long time Hemolysis or rate of hemolysis is also linear with the rate of bubbling After thinking about this air delivery which Dr Clowes brought out we compared the rate of hemolysis using warm saturated oxygen with its rate using dry oxygen we found about 40% reduction in the rate of hemolysis using warm "wet-oxygen"

We also wondered about toxicity of 100% oxygen and live red cells We know it is toxic to those cells under long exposure but there was no bubbling up to one hour when we used warm oxygenated air

DR HUGH F FITZPATRICK, New York I would like to make a very simple but practical suggestion for those who are working with the Sigmamotor pump It is well known at the University of Minnesota,

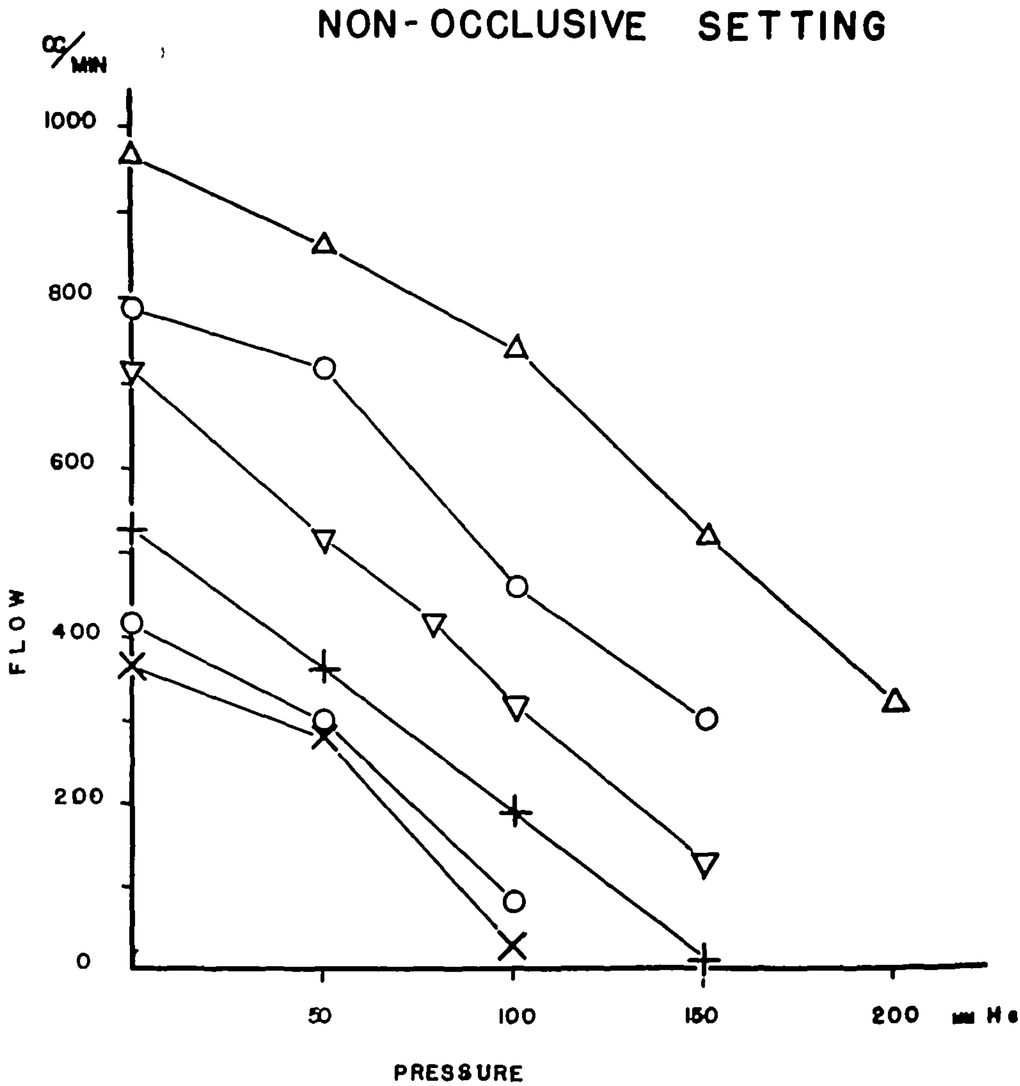


FIG 43 Effect of variations in "occlusive" pressures on flow rate when using Sigmamotor pump (Dr Fitzpatrick)

but I am afraid is not known by those just starting to work with this pump

The pump should be occlusive This problem is important because we wasted many months in not properly adjusting the Sigmamotor pump The pump is designed to be an occlusive one, and only if so adjusted will the flow remain constant against pressure Figure 43 shows the influence of resistance on the flow with the pump non-occlusive As one can see, if the pressure to the flow increases, the flow decreases considerably This simple problem bothered us for many months as we were studying dogs at what we thought was 30% flow with an improperly adjusted pump Consequently, we were actually running a very low

flow and as a result we had a very high animal mortality Figure 44 shows that when the pump is properly adjusted and is occlusive one attains a constant flow in spite of pressure up to 200 mms of mercury

DR HANS C ENGELL, Copenhagen At the University of Copenhagen we have for the last year and a half worked with a disposable oxygenator utilizing the portable perfusion equipment We also want to design a disposable unit Again a suitable form seems to be the use of the bubble diffusion principle This new oxygenator is equipped with synchronous nylon filters that defoam Our oxygenator is suspended in a plastic case in the heart lung machine

This is another type of the bag oxygenator which is used 4 5 l per

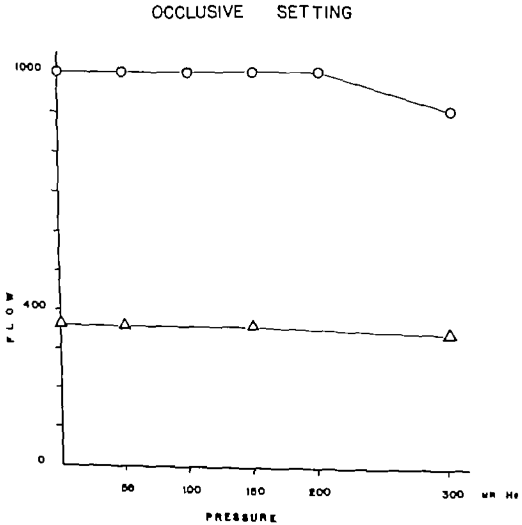


FIG 44 Occlusive setting at constant resistance is necessary to uniform flow rate with Sigmamotor pump (Dr Fitzpatrick)

minute This is one type of bag used for dog experiments There is an extra section which we call the calibrator for the introduction of nitrogen, CO_2 and gases for anesthesia

We had to make some further experimentation in the investigation of minute bubbles to see if it were possible to get rid of these minute bubbles We tried bubble traps in experiments with blood, but it was not possible to demonstrate bubbles in this way Then we used human plasma To demonstrate minute bubbles we made some holes in the plastic sheet Then small bubbles under certain conditions could be occasionally seen directly or by the magnifying glass In these experiments we could demonstrate that every kind of bubble oxygenator had equal flow which always resulted in bubbles in the blood

DR STANLEY J SARNOFF, Bethesda I should like to know if anyone has experimented on the difference between dog and human blood Secondly, I think one of the very important points that came out was Dr Kolff's opinion on O_2 intoxication which was substantiated by Dr Kaplan's findings Would it be the consensus that Dr Kolff should review oxygen intoxication since it is known that a human exposed to oxygen for 12 hours will continue to have CO_2 in the blood?

DR WILLEM J KOLFF Cleveland In the German *Handbuch Der Inneren Medizin,* VI/2, 1954, revised by G v Bergmann, W Frey and H Schwiegk, there is a short summary about oxygen intoxication Over-oxygenation is brought about nearly always by forcing the animals to breathe oxygen under high tension which results in cerebral symptoms and convulsions and the like and will later result in pulmonary damage Strangely enough if you have very high oxygen tension in your plasma your oxyhemoglobin does not get reduced, you are limited in the transport of CO_2 for which reduced hemoglobin is very important I am quite sure that our reason for looking into this was stimulated by Doctor Kirklin I understand that in the past we, as well as Doctor Kirklin, have seen patients where everything appeared all right and everybody was quite happy at 7 or 11 p m , and yet at 4 a m the patient for some unknown reason did not do well Some showed cerebral damage, one showed very strange mottling over the body Since we have used the polarograph to avoid over-oxygenating, we have seen none of these complications

QUESTION In the Handbuch, what was the time limit given?

ANSWER (Dr Kolff) I recall that two hours of pure oxygen is the upper limit for man, that is breathing pure oxygen under normal pressure

DR JAMES V MALONEY Los Angeles I would like to make a comment or two During one tour of duty with the Army we were interested in oxygen tensions in pilots breathing pure oxygen During a later tour of duty with the Navy we were interested in oxygen tension in divers and submarine crews There was an enormous amount of money spent after the war up to 1949 investigating oxygen tension and it was pretty well concluded that oxygen intoxication is not a serious problem under the conditions encountered in pump-oxygenators of the types used in surgery at this time

DR. STANLEY J SARNOFF National Heart Institute I think that since the maximum pressure we are working on is 750 mm Hg oxygen poisoning as a serious problem can be eliminated

DR JOHN W KIRKLIN Rochester I rise to the question that perhaps conditions may occur during cardiotomy which are not the same as seen in the intact man For instance the intact man oxygenates blood at normal temperature In most oxygenators oxygenation does not occur at body temperature Blood pO_2 in an oxygenator at 29° C might become significantly higher when it is suddenly increased to 38°C I think also one has to take into consideration the possibility that blood with a pO_2 of 690 mm Hg at 29°C would be suddenly increased when exposed to temperature of 38°C and might produce oxygen damage I think there is no evidence that high oxygen tension during extracorporeal perfusion is deleterious We all should look into this problem, because there is some evidence that it might be a factor which causes damage during perfusion at lower temperatures (29-30°C) or with pO_2 change

DR. FRANK GERBODE, San Francisco In regard to the question of oxygen toxicity I should like to mention that we have carried approximately three hundred patients having valvotomies or other cardiac procedures on one hundred per cent oxygen alone using no inhalation anesthetic and only occasionally pentothal or intravenous demerol We have no evidence of oxygen toxicity This came about because I wished to keep the myocardium as pink as possible As long as the retractor is not moved or the bronchi stimulated, the patient remains quiet

There is a difference between exposing blood to oxygen directly and administering oxygen through an endotracheal tube The former may cause high oxygen tensions the latter not

This leads me to another aspect of the whole problem of oxygenating

minute This is one type of bag used for dog experiments There is an extra section which we call the calibrator for the introduction of nitrogen, CO_2 and gases for anesthesia

We had to make some further experimentation in the investigation of minute bubbles to see if it were possible to get rid of these minute bubbles We tried bubble traps in experiments with blood, but it was not possible to demonstrate bubbles in this way Then we used human plasma To demonstrate minute bubbles we made some holes in the plastic sheet Then small bubbles under certain conditions could be occasionally seen directly or by the magnifying glass In these experiments we could demonstrate that every kind of bubble oxygenator had equal flow which always resulted in bubbles in the blood

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surprised that no one has spoken of this Kety has shown that intra atrial arterial CO_2 tension is the strongest determinant of cerebrovascular resistance A low CO_2 tension (25 mm Hg) results in an increased cerebrovascular resistance When a low arterial CO_2 tension is accompanied by hypotension cerebral blood flow diminishes markedly Thus a normal CO_2 tension may be said to permit cerebrovascular dilatation during periods of hypotension

If CO_2 is not added to the oxygenator a marked respiratory alkalosis occurs with CO_2 "washout" This occurred in four patients in our series In spite of arterial oxygen saturations of over 100% and arterial blood pressures comparable to those of other patients in this series These patients demonstrated signs of temporary impairment of the central nervous system e g a disturbingly low tolerance for anesthesia following bypass and delay in recovery from anesthesia In one case during bypass the arterial pCO_2 was 13 mm Hg Fortunately none of these patients manifested permanent central nervous system damage

Recently in this series we have been monitoring CO_2 tensions indirectly by continuous analysis of the gaseous mixture at the arterial end of the oxygenator In this manner we are able to maintain blood pCO_2 at 40 (± 1) mm Hg by the addition of adequate CO_2 to the oxygenator

In all other cases except the above mentioned four an arterial pCO_2 of 30-40 mm Hg has been maintained during by pass and there has been no evidence of decreased cerebral circulation during or after bypass

DR GEORGE H A CLOWES JR Cleveland O Doubtless we shall hear more of carbon dioxide tomorrow In contrast to oxygenators dependent upon a direct gas blood interface for diffusion the membrane oxygenator does not tend to wash out CO_2 from the blood In fact, carbon dioxide tension rises unless the blood is being delivered at a level of more than 85% oxygen saturation This means that a fixed arterial pCO_2 is established for each oxygenator during a given perfusion If the area of membrane is adequate to oxygenate the blood hypercapnea will not develop

I agree with Dr Bahnson in the disposability of oxygenators All parts of the membrane oxygenator which touch blood are thrown away We have seen non wettable membranes become wettable by the deposit of a very thin layer of protein substance on them This does not seem to interfere with oxygenation nor does it seem to trap thrombocytes or leucocytes Dr Kolff with his coil membrane oxygenator found about the

blood on film oxygenators I presume many of you have noticed that occasionally the film characteristics of the blood may be quite different, affecting the ease with which it can be oxygenated Are the differences due to variations in the composite proteins present, or may it not even be related to the diet of the donor? Believing that having a slightly higher fat content might improve the filming characteristics, I suggested several months ago that we should allow the donors to eat before taking their blood It is our impression that the blood does film better under these conditions than when the donor has been starved

DR JOHN F PERKINS, JR, Chicago I can contribute very little to oxygen toxicity This problem Dr Kolff brought out is very interesting As the blood is warmed upon entering the body from the pump-oxygenator, the oxygen tension must rise in the blood as the result of the warming process, because the hemoglobin will not hold the same amount of oxygen as it did at a lower temperature This might cause a rise of from say 600 to 700 mm in the oxygen tension of the blood

Not much is known about the basic mechanisms of oxygen toxicity I think there is some evidence that peroxides are being formed as in radiation sickness This may cause cerebral edema Dr Kenneth Penrod has shown that inhalation of oxygen causes pulmonary atelectasis in rats I think we can separate out the atelectatic damage of the lung in the pump-oxygenator situation because the lung is empty during perfusion We could consider other factors possibly related to oxygen toxicity such as cerebral damage, which certainly should be investigated

DR DAVID MENDELSOHN, Cleveland, O First of all, I feel that I must say a word on oxygen toxicity We, as has Dr Kolff, have been using a Kay-Cross oxygenator, and have the largest clinical series in which this machine has been used exclusively Since February of this year, we have monitored oxygen tension, utilizing the Clark oxygen polarograph In all cases prior to bypass, the O_2 tension in the oxygenator has been high (over 400 mm Hg) Frequently, during bypass, especially with small children, we have observed very high O_2 tension in the arterial blood We have seen no evidence of oxygen toxicity, neither cerebral nor respiratory, in the postoperative period If the patients deteriorated postoperatively the cause was quite clear and usually related to a defect in circulatory dynamics

We have been interested in CO_2 tension during perfusion I am

surprised that no one has spoken of this Kety has shown that intra atrial arterial CO_2 tension is the strongest determinant of cerebrovascular resistance A low CO_2 tension (25 mm Hg) results in an increased cerebrovascular resistance When a low arterial CO_2 tension is accompanied by hypotension cerebral blood flow diminishes markedly Thus a normal CO_2 tension may be said to permit cerebrovascular dilatation during periods of hypotension

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same degree of cell destruction or disappearance as that observed by us However, this deposit is hard to remove and may be a source of serious trouble unless thrown away

I do agree with those who want some standardization of terms and values But I think that certain physiological standards are necessary first What damage is done to the blood? What damage if any does perfusion cause? What is the survival rate with prolonged total perfusions?

DR HUGH H BENTALL, England It is rather surprising to be called on I had no intention of standing before you and talking about oxygenators I know it is a very dangerous topic to take a stand on

We have been working with the Melrose oxygenator in London for the last six years I think it may be of help to those of you who are not as advanced as the leaders in this field—and we are certainly not—to indicate some of the thinking which caused us over the years to modify our apparatus and the way we use it At the outset the ideal seemed to be a fully automatically controlled apparatus This was quite successfully achieved The peak of such apparatus is seen in the present machine at Rochester Can we not have a simplified and automatically controlled apparatus in such a way that the machine becomes self-regulating and less dependent on electricity or mechanical ingenuity? I am sure we can The way we have been modifying the apparatus has been first in employing gravity drainage There is no mystery in gravity, it is a method of continuous suction It minimizes the difficulty of venous flutter and overcomes the difficulty of collapse of the vena cava over the venous line It is not as self-regulatory as the apparatus of Dr Clowes with his fixed volume content which is self-regulatory as long as no blood is lost from the patient

The oxygenator we are using is the type devised by Dr Melrose which oxygenates blood up to 4 liters per minute This is not the ideal to be achieved, but it has the merit of a low priming volume

I want to ask a question Can we really agree on parameters for comparison in pumps? This has been stressed before I would say that we should set up some definite ideas with respect to pumps and oxygenators, and let the Committee arrive at some definite instructions for all of us who use them There were many good ideas presented today which, if used, may succeed in displacing some of the older apparatus

THE PHYSIOLOGY OF PERFUSION

SECTION II

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THE PHYSIOLOGY OF PERFUSION

SECTION II

WHAT IS ADEQUATE PERFUSION?

By

JOHN W KIRKLIN, M D., DWIGHT C McGOON, M D.,
ROBERT T PATRICK, M D , *and* RICHARD A THEYE, M D

FOR PURPOSES of open intracardiac surgery whole body perfusion is considered adequate when it allows accurate unhurried operation and recovery of the patient Discussion of adequacy of perfusion in terms of flows pressures saturations and the like is incomplete unless these variables can be related to the establishment of good operating conditions and to survival of patients without ill effect from perfusion

It is recognized that one surgeon s opinion as to good or poor operating conditions may not be shared by another Likewise in review of a series of cases identification of imperfect perfusion as a cause of death in certain of the nonsurviving patients must in part, be a matter of opinion In spite of this it is felt that a discussion of adequacy of perfusion based upon clinical experience might be advantageous at this time

MATERIAL AND METHODS

The first 245 patients operated upon with perfusion on one surgical service at the Mayo Clinic form the basis for this discussion Open intracardiac surgical treatment was the indication for perfusion in all The operations were done between March 23 1955 and August 24 1957 The anatomic diagnoses are shown on page 137 Ages varied between two and one half months and forty seven years The spectrum of patients subjected to surgical treatment has remained unchanged throughout the series The type of cases in the group of patients with ventricular septal defect has been previously described [1]

Light ether anesthesia and bilateral anterior thoracotomy were employed in all cases Basic technic for cannulation was standard

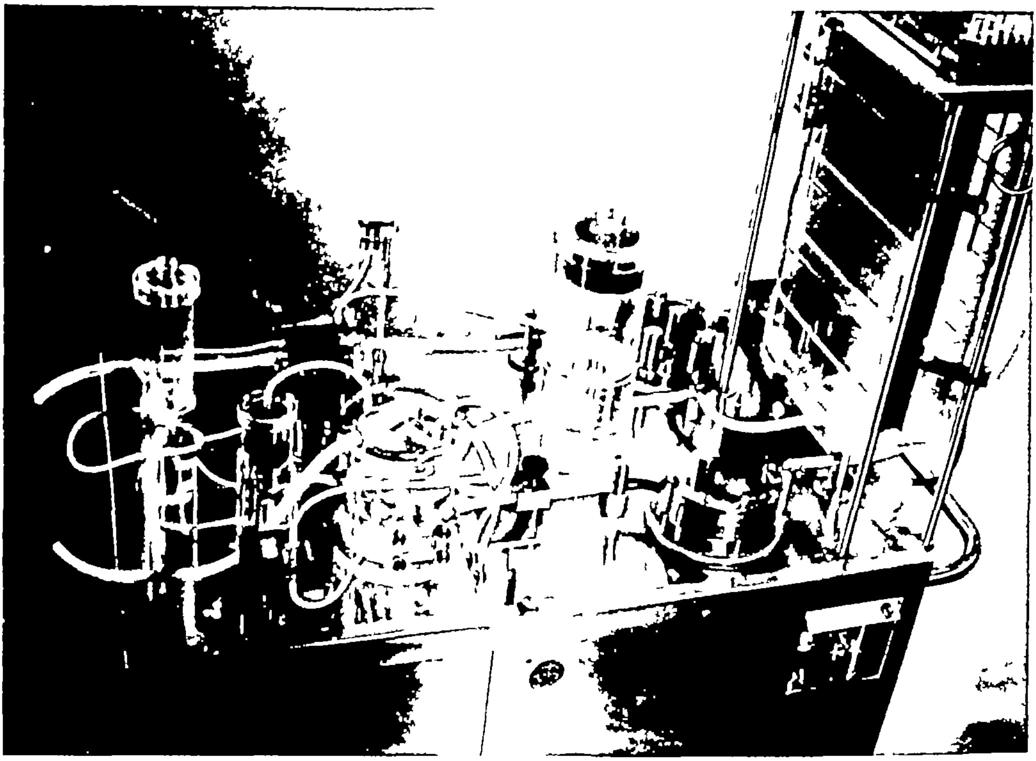


FIG 45 Modified Gibbon-type pump-oxygenator

throughout,[2] and included insertion of the arterial cannula into the aorta through the previously divided subclavian artery Each 500 cc of donor blood contained 15 mg of heparin Heparin was administered intravenously to the patient just prior to cannulation, in a dose of 3 mg per kilogram of body weight, except late in the series when the dose in adult patients was changed to 90 mg per square meter of body surface Protamine was given intravenously to the patient when the heparin effect was no longer needed, in the same dosage as used for the heparin

A modified Gibbon-type pump-oxygenator[3,4] was employed for all perfusions (Fig 45) The conduct of perfusion in early cases was based upon the laboratory experience that preceded clinical application Certain alterations have been made in the conduct of perfusion during this experience, based upon changing concepts, clinical experience, laboratory data and the reports of other workers

The record of each patient in the series has been carefully reviewed Necropsy was performed in all patients who died save

one Evidence of possible ill effects of perfusion has been sought in each surviving patient

Each death has been classified as either related to perfusion or not In certain cases the assignment of cause of death is difficult but it is believed that in light of present knowledge the separation into perfusion and nonperfusion deaths can be effected with reasonable accuracy A perfusion death is one considered related to the perfusion itself or to any part of the surgical anesthetic or supportive management necessitated by the use of the pump-oxygenator Deaths considered not related to perfusion include those from heart block and from grossly inadequate repair Chronic heart failure irreducible pulmonary hypertension and severe pulmonary vascular changes were present in some patients in both categories but were not considered in themselves adequate explanation for death

ANALYSIS OF SELECTED GROUPS

It is probably unwise to attempt evaluation of adequacy of perfusion for intracardiac operations in general from analysis of results in selected groups of cases Low mortality figures for repair of a relatively simple defect might obscure the possibility that the deaths although few were in fact related to perfusion For example repair of uncomplicated atrial septal defect can be stated to have an inherent operative mortality which is extremely low Evidence for this is the fact that 119 patients with uncomplicated atrial septal defect have been operated upon by the atrial well technic with two deaths a mortality rate of approximately 2 per cent[*] Thus in repair of atrial septal defect utilizing extracorporeal circulation a mortality figure significantly in excess of this even though still low must be suspected of reflecting a perfusion that was not adequate for the patients in the group who died

Also mortality figures gratifyingly low for a selected operation do not necessarily give assurance that a similar perfusion will allow a similar low perfusion mortality for a more complex operative procedure The results of operation for ventricular septal defect when viewed alone might be misleading as to adequacy of perfusion for these patients and as to the safety in application

of a similar perfusion to a more difficult and prolonged operation such as repair of the tetralogy of Fallot In the first twenty cases of ventricular septal defect operated upon by us there were four deaths, a mortality rate of 20 per cent At that time it was felt that the four deaths were not related to perfusion, but were more likely related to the severity of the pulmonary hypertension and previous cardiac failure Viewed from present perspective, it is nearly certain that three of the four deaths were directly related to perfusion This seems supported by the fact that in the last 30 operations for ventricular septal defect in this series the mortality rate has been reduced to 7 per cent

ANALYSIS OF TOTAL SERIES

All patients in the series are depicted in Figures 46, 47 and 48 In these, patients are grouped for reasons indicated in the legend for Figure 46 The case number of a patient identifies his position on these charts

No surviving patient has any demonstrable ill effects from perfusion with the exception of three operated upon during a period when Pseudomonas infections were occurring These will be noted later

Miscellaneous Perfusion Deaths.—In Figure 46, all deaths related to perfusion are so indicated Of these, all but seven are from pulmonary complications or from a syndrome of apparently sudden death These two categories are discussed in detail later Seven of the perfusion deaths are from miscellaneous causes

1 *Hemorrhage* —One of these 245 patients (case 15), a nineteen-year-old girl with tetralogy of Fallot, died eight hours after operation from massive continuing hemorrhage In this case, previously described by us,[6] there was an extremely high plasma hemoglobin content in the mixed blood prior to its circulation in the pump-oxygenator, suggesting blood incompatibility as a cause of the fatal hemorrhagic diathesis

Adequate perfusion must not result in severe postoperative bleeding The avoidance of blood trauma in the pump-oxygenator, the use of large arterial cannulae if large flows are employed, careful surgical technic and precise cross-matching of blood are important to the prevention of this complication

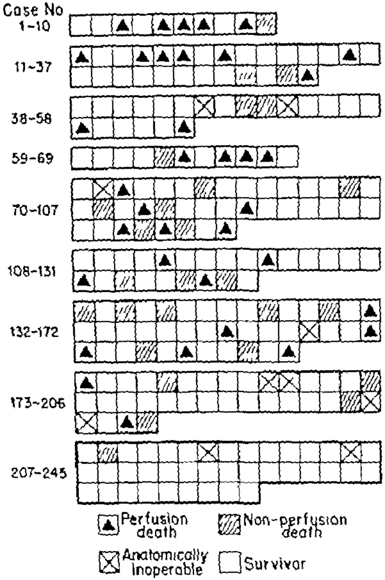


FIG. 46 *Schematic representation of deaths related to perfusion In this* and Figures 47 and 48 cases are in nine groups In cases 1 to 10 the perfusate consisted in part of 3.5 per cent solution of polyvinyl pyrrolidone thereafter use of this substance was discontinued After case 37 certain measures described in the text were taken to prevent pulmonary complications Cases 38 through 58 as a group were followed by a small group (cases 59 through 69) in which significant overloading with blood occurred. Cases 70 through 107 and those in preceding groups were operated upon without induced cardiac arrest In the group of cases 108 through 131 and the groups thereafter potassium-induced cardiac arrest was employed for all operations in the ventricles, and for certain other procedures Cases 132 through 172 and those thereafter are cases in which operations were performed after the cardiovascular service was transferred from one of the hospitals associated with the Mayo Clinic to the other Late in the group of cases 132 through 172, Pseudomonas infection appeared, and the entire procedure for sterilization of the apparatus was altered for cases after case 172 Following the group of cases 173 through 206 final measures were taken to provide the desired oxygen tension in the arterial blood

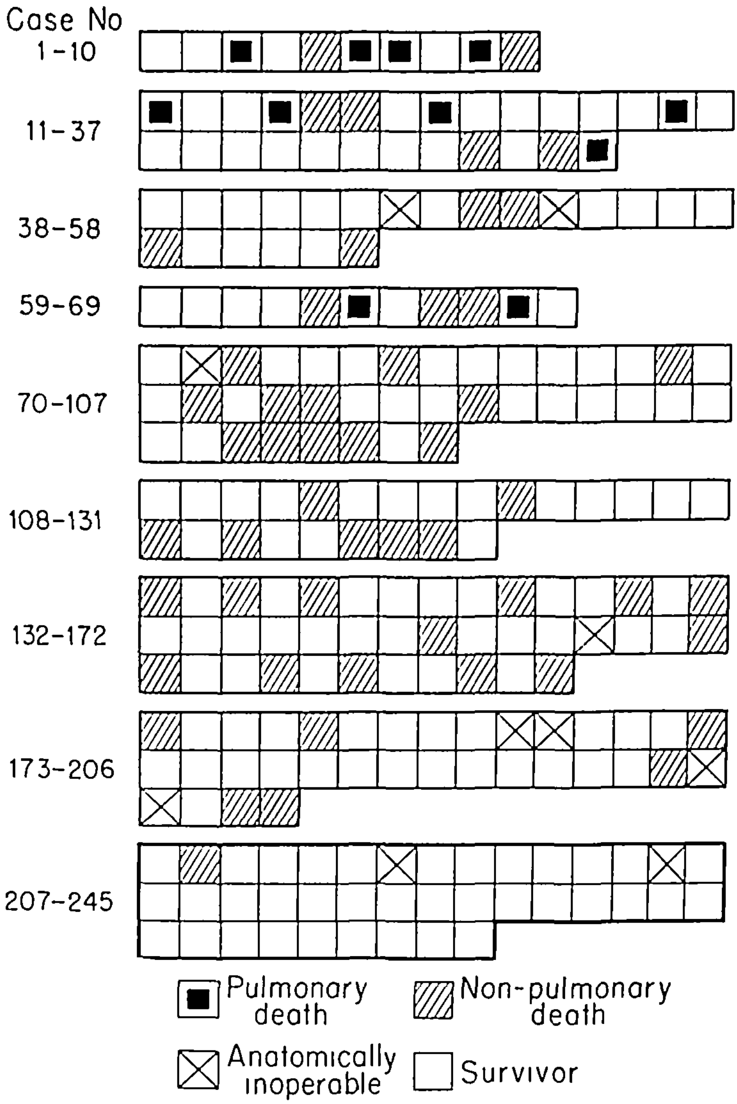


FIG 47 Schematic representation of deaths from pulmonary complications

2 *Unexplained Persisting Hypotension*—A patient with tetralogy of Fallot (case 117) died fourteen hours after operation with progressing hypotension refractory to treatment An adequate cause for this was not demonstrated either at necropsy or at careful review of the record

3 *Hypovolemia*—Two infants (cases 5 and 58) died shortly after extracorporeal circulation was discontinued There is excellent evidence that both had become profoundly hypovolemic during perfusion as a result of inadequate replacement of blood lost during the period of cardiopulmonary bypass

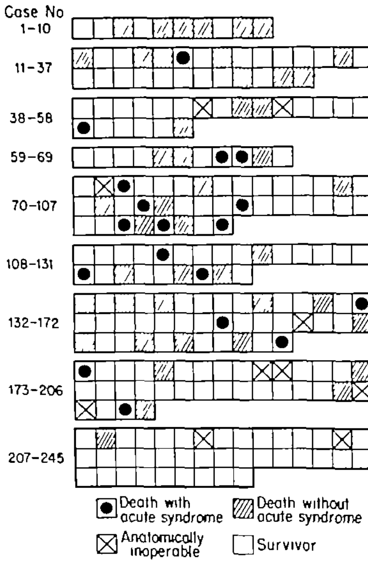


FIG 48 Schematic representation of deaths from acute syndrome of apparently sudden death

4 *High Venous Pressure During Perfusion* —One patient (case 162) a twelve year-old boy with a complete form of common atrioventricular canal died probably from the effects of extremely high superior vena caval pressure during perfusion Up until the time of this operation venous pressure in the lower extremity was regularly monitored but that in the upper extremity only on occasions and not in this instance During perfusion this patient s face was noted to be very cyanotic and at the end of the operation his face and upper extremities were covered by petechiae The

patient never regained consciousness and died one hour after operation. Although the electroencephalogram was normal during perfusion and the brain showed only cerebral edema at necropsy, the clinical picture which was unique in this case seems best explained by severe obstruction of venous return from the upper part of the body.

Venous pressure during whole-body perfusion is related to blood volume, rate of flow, and resistance imposed by the structures serving as route of transfer of venous blood from the body to the pump-oxygenator. In the presence of normal blood volume and a flow rate during perfusion approximating normal, the size and method of positioning of venous cannulae are of critical importance as regards venous pressure. Very large cannulae, placed so that the ends lie just within the superior and inferior cava, are now employed. As a precaution, since the experience in case 162, venous pressure is continuously monitored from a vein in an upper extremity and intermittently from a vein in a lower extremity during operation.

5. *Bacterial Contamination.*—Until its occurrence in case 161, there had been no minor or major infection save that in case 116, in which Pseudomonas meningitis developed fifteen days after operation. A complete cure of this was effected by polymyxin given intrathecally. However, patients 161 and 167 died twenty-eight days and eighteen days after operation from Pseudomonas bacterial endocarditis. Three other patients operated upon in the same period as these developed Pseudomonas bacteremia, two dying one month after leaving the hospital and the other still living although harboring endocarditis.

In view of this evidence of inadequacy of the sterilizing procedures used until this time, changes were made. Since the operation in case 172, the parts of the pump-oxygenator have been individually sterilized and then assembled with strict aseptic technic just prior to operation. All parts are autoclaved except the few lucite ones, which are immersed in 10 per cent formaldehyde for two hours. Since the introduction of this technic, no further infections have occurred and cultures which are routinely taken from the machine have been negative.

Pulmonary Complications.—Pulmonary complications were a

common cause of death and morbidity in patients operated upon early in this series The clinical picture produced by these was clear Most often there was profuse tracheobronchial secretion, occasionally occurring immediately after operation At times the secretion was bloody at times frothy and at times thick and tenacious Coarse and fine rales could be heard and the roentgenogram of the thorax often showed diffuse mottling and at times lobar atelectasis When these complications were fatal death occurred one to six days after operation Necropsy showed the lungs to contain multiple areas of collapse hemorrhage and edema

Such complications occurred more often in patients with severe pulmonary hypertension than in others but were not limited to them On the basis of considerable evidence it is believed that these pulmonary complications result from inadequate perfusion not from the condition of the heart or lungs of the patient prior to perfusion

Study of Figure 47 shows that operation and perfusion can be conducted so as to prevent pulmonary complications This figure shows that deaths attributable to them were frequent in our early experience but have not occurred since the one in case 68 In the last 177 cases there has been neither death nor unusual morbidity from pulmonary complications The postoperative care of these patients has been identical to that of other patients undergoing thoracotomy

Certain measures appear to have been important in eliminating pulmonary complications First, during cardiopulmonary bypass the lungs are motionless but gently inflated with a gaseous mixture of 50 per cent oxygen and 50 per cent helium The introduction of this measure in the fall of 1955 followed the suggestion of Gibbon and others that high oxygen tension might rapidly damage the alveoli of the lung which has no pulmonary blood flow Second also in the fall of 1955 in order to prevent the escape of even small amounts of fluid into tissues during perfusion the perfusate was given a more normal colloidal osmotic pressure by the addition of appropriate amounts of concentrated serum albumin to compensate for the normal saline solution used as a

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Supplied through the courtesy of the American Red Cross.

patient never regained consciousness and died one hour after operation Although the electroencephalogram was normal during perfusion and the brain showed only cerebral edema at necropsy, the clinical picture which was unique in this case seems best explained by severe obstruction of venous return from the upper part of the body

Venous pressure during whole-body perfusion is related to blood volume, rate of flow, and resistance imposed by the structures serving as route of transfer of venous blood from the body to the pump-oxygenator In the presence of normal blood volume and a flow rate during perfusion approximating normal, the size and method of positioning of venous cannulae are of critical importance as regards venous pressure Very large cannulae, placed so that the ends lie just within the superior and inferior cava, are now employed As a precaution, since the experience in case 162, venous pressure is continuously monitored from a vein in an upper extremity and intermittently from a vein in a lower extremity during operation

5 *Bacterial Contamination* —Until its occurrence in case 161, there had been no minor or major infection save that in case 116, in which Pseudomonas meningitis developed fifteen days after operation A complete cure of this was effected by polymyxin given intrathecally However, patients 161 and 167 died twenty-eight days and eighteen days after operation from Pseudomonas bacterial endocarditis Three other patients operated upon in the same period as these developed Pseudomonas bacteremia, two dying one month after leaving the hospital and the other still living although harboring endocarditis

In view of this evidence of inadequacy of the sterilizing procedures used until this time, changes were made Since the operation in case 172, the parts of the pump-oxygenator have been individually sterilized and then assembled with strict aseptic technic just prior to operation All parts are autoclaved except the few lucite ones, which are immersed in 10 per cent formaldehyde for two hours Since the introduction of this technic, no further infections have occurred and cultures which are routinely taken from the machine have been negative

Pulmonary Complications —Pulmonary complications were a

Two patients aged ten weeks and twelve weeks with ventricular septal defect were successfully operated upon during the time these deaths were occurring and are alive and cured today The syndrome seemed more prone to occur in patients who had been very ill prior to operation The adoption of induced cardiac asystole seemed not to affect its incidence

Perfusions for the group of cases 132 through 172 and 173 through 206 were by our present standard reasonably adequate as regards flow rate venous and arterial pressures per cent saturation of hemoglobin in venous and arterial blood temperature of perfusate and patient and blood volume The incidence of deaths from the acute syndrome had decreased to 7 per cent in these two groups Its persistence even at this low rate however was unacceptable

In the last group of this report cases 207 through 245 and in subsequent cases measures were taken to maintain oxygen tension in the arterial line between 100 and 250 mm of mercury The relation between per cent saturation and oxygen tension in whole blood was reviewed in the previous report given at this conference When gaseous flow into any efficient oxygenator is the same prior to establishment of perfusion as it is during perfusion, opportunity exists for the development of very high oxygen tension in the arterialized blood Since the operation in case 206 control of oxygen tension at the start of perfusion has been achieved by using a gas flow through the oxygenator of room air with added carbon dioxide until three minutes before perfusion actually begins Then a mixture of 97 per cent oxygen and 3 per cent carbon dioxide is employed. Control of oxygen tension during perfusion has been accomplished by using the oxygenator in the manner previously described at this conference [4]

In the last group (cases 207 through 245) there has been no death from the acute syndrome and indeed no death from perfusion This increased safety of perfusion has not been accomplished by shortening the perfusions for in our hands the complete and accurate repair of ventricular septal defect tetralogy of Fallot and common atrioventricular canal continues to be time consuming The average perfusion time in this last group of

vehicle for the heparin employed in each bottle of heparinized blood These measures seemed efficacious in the group of cases 38 through 58, but in the next group of cases (59 through 69), in which gross overloading of the patient with blood is known to have occurred, there were two deaths from pulmonary complications Since that time, the avoidance of hypervolemia during and after perfusion has also been considered essential to adequate perfusion

Acute Syndrome of Apparently Sudden Death.—After the elimination of pulmonary complications as a cause of death following perfusion, it became apparent that certain patients in whom the operation and perfusion had seemed satisfactory, nonetheless died In spite of an inability at that time to identify the factors contributing to the deaths, it seemed that they were related to perfusion The deaths were often sudden and part of a syndrome

This syndrome consisted of apparently sudden death, early after intracardiac operation done with the aid of extracorporeal circulation Usually the patient appeared to be convalescing satisfactorily until trouble struck The symptoms most often appeared in the first twelve hours and very occasionally in the first hour after operation They sometimes occurred as late as thirty-six hours after operation The syndrome was often preceded by a brief period of restlessness, and in some instances by systemic hypertension of moderate degree The catastrophe itself seemed ushered in by the abrupt appearance of deep, gasping respirations with prominent employment of accessory muscles of respiration Moderate cyanosis was sometimes noted After a brief but variable period, the previously alert and responsive patient appeared suddenly comatose and respiration became feeble and shallow Blood pressure and pulse usually showed no striking change until a few minutes later when respiration had virtually ceased, following which the heart beat slowed and then stopped

Inspection of Figure 48 shows that deaths from this acute syndrome occurred sporadically until recently Although patients less than three years of age seemed more prone to have this syndrome, it was not limited to them nor did it inevitably occur in them

blood and seems adequate Arterial pH is 7 30 to 7 40 Arterial blood temperature in the pump-oxygenator is 33°C and while not ideal, appears at present adequate The patient s body temperature during perfusion is usually between 35° and 37°C

On the basis of the experience presented and because of the absence of mortality related to perfusion in the last group comprising thirty nine cases it is believed that perfusions conducted in the manner described are at present adequate

TABLE I

DISTRIBUTION OF CASES BY ANATOMIC DIAGNOSES

Malformation	*Cases*
Ventricular septal defect	110
Tetralogy of Fallot	52
Common atrioventricular canal	18
Pulmonary stenosis	12
Atrial septal defect with associated conditions	11
Atrial septal defect, uncomplicated	7
Total anomalous pulmonary venous connection	6
Congenital aortic stenosi	5
Single ventricle	5
Single atrium and cleft mitral valve	3
Origin of both vessel from right ventricle	2
Ruptured aneurysm of sinus of Valsalva	2
Mitral stenosis	1
Congenital combined subvalvular aortic and pulmonary stenosis	1
Miscellaneous inoperable lesions	10
Total	245

Complex malformations which seem anatomically irreparable by present technic.

REFERENCES

1 DuShane J W Kirklin J W Patrick, R T Donald, D E Terry H R., Jr Burchell, H B and Wood E H Ventricular septal defects with pulmonary hypertension Surgical treatment by means of a mechanical pump-oxygenator *J.A.M.A.* 160 950-953 1956

2 Harshbarger H G Kirklin J W and Donald, D E. Studies in extracorporeal circulation IV Surgical techniques *Surg Gynec & Obst* (In press)

3 Jones R. E Donald, D E Swan H J C Harshbarger H G., Kirklin J W and Wood E H Apparatus of the Gibbon type for mechanical bypass of the heart and lungs A preliminary report *Proc Staff Meet Mayo Clin.*, 30 105-115 1955

thirty-nine cases in which there has been no mortality from perfusion has been forty-eight minutes, with extremes of twenty-one minutes and ninety minutes The one death in the group of operable patients resulted from a Stokes-Adams episode on the twenty-third postoperative day in a boy with complete heart block subsequent to operation

COMMENT

Extreme emphasis must be placed on the possibility that perfusions conducted in a manner totally different from that defined herein as adequate may be also, in every way, adequate and desirable It is only possible at this point to define the perfusion for open intracardiac operations that would be considered by us adequate for the patients being operated upon in our institution

Flow rates of approximately 2 3 liters per minute per square meter of body surface are used at present and are considered adequate Early in our experience flow rates of 75 cc per minute per kilogram of body weight were considered adequate Moffitt's[7] study of these early cases and his expression of flow rates as liters per minute per square meter led to the realization that such flows did *not* approximate the cardiac output of the lightly anesthetized patient prior to perfusion The present flow rates do Steady flow rates in the neighborhood of 2 3 liters per minute per square meter of body surface are at present achieved by maintenance of a normal blood volume, by the proper positioning of large-diameter venous cannulae and by the present mode of operation of the pump-oxygenator

With such flows, and with the ascending aorta cross-clamped during induced cardiac asystole, mean aortic pressures within ten minutes after start of perfusion usually are only 5 to 10 mm of mercury less than those prior to cardiopulmonary bypass Venous pressures are ordinarily between 10 and 20 mm of mercury

Blood oxygen tension of 100 to 250 mm of mercury in the arterial line is considered desirable During these perfusions, venous saturation is between 70 and 80 per cent Carbon dioxide tension between 30 and 40 mm of mercury is achieved in arterialized

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4 Kirklin, J W , Theye, R A and Patrick, R T The Stationary Vertical Screen Oxygenator Read before the Work Conference on Problems of Extracorporeal Circulation, Chicago, Illinois, Sept 20-22, 1957
5 Kirklin, J W , Ellis, F H , Jr , and McGoon, D C Unpublished data
6 Kirklin, J W , Donald, D E , Harshbarger, H G , Hetzel, P S , Patrick, R T , Swan, H J C and Wood, E H Studies in extracorporeal circulation I Applicability of Gibbon-type pump-oxygenator to human intracardiac surgery 40 Cases *Ann Surg*, 144 2-8, 1956
7 Moffitt, E A Unpublished data

FLOW METERS

By

IAN K. R. McMILLAN

FOREWORD

I WOULD LIKE to start by thanking the National Institutes of Health, and its Surgery Study Section as the organizers of this congress which I am sure is unique for its comprehensive review of the field of extra-corporeal circulation in relation to surgery. Secondly I would like to thank them for their invitation to attend the congress and to present this paper.

INTRODUCTION

This report concerns the clinical use of flow meters in this field and as my knowledge of their electronic details is negligible I shall describe the various types and comment on them to the extent that I can. I hope this will stimulate discussion of the merits and demerits of the various instruments by those groups using them.

Descriptions of the machines discussed can be found in the literature described by their original designers and users.

I think we are all agreed that the flow or output of a heart lung machine is the basic factor in its performance. The discussion of the optimum rate of flow for a perfusion has been dealt with elsewhere in this meeting. However a knowledge of the flow at any time is in my opinion vital information whatever the design of the pump. It does not matter whether the pump has been set to a predetermined flow rate or whether the output is governed entirely by the venous return, it is desirable to know what the output is at any time. In addition, and most important, it is a sensitive index of trouble during the course of the perfusion.

If two flow meters are available so that input and output can

4 Kirklin, J W , Theye, R A and Patrick, R T The Stationary Vertical Screen Oxygenator Read before the Work Conference on Problems of Extracorporeal Circulation, Chicago, Illinois, Sept 20-22, 1957
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7 Moffitt, E A Unpublished data

urements being recorded, in particular the venous and arterial pressures as changes in one will always be reflected to some degree in the other two

DISADVANTAGES OF A FLOW METER

(a) It is a machine and one should be aware of the limitations of the particular type chosen

(b) It is an extra piece of apparatus and an extra dial or screen to watch I believe a factor in this field is to keep the system as simple as possible and so to reduce the possibility of error

(c) A flow meter means the introduction of something further into the pump circuit and this in its turn leads to attention to details such as the avoidance of clotting which may alter the machine's base line Coagulation will probably be dealt with by the heparinization of the patient and other measures such as siliconizing the apparatus

(d) Finally why have a flow meter at all? If the pump is accurate and remains so throughout perfusion, it can be argued that predetermined settings are all that are required but this point will be discussed later

REQUIREMENTS OF FLOW METERS

This paragraph lists the requirements of a flow meter and I must emphasize that no machine yet produced is perfect by my criteria.

1 The machine should be robust and able to record accurately for long periods of time

2 It must not interfere with the smooth working of the pump circuit or alter the flow through the tubes

3 It should not encourage clotting or at least no more so than any other part of the circuit

4 It follows from item 3 that if possible all its surfaces should be smooth and with no sudden changes to become a source of extra haemolysis due to constriction or other physical factors

5 It should have a steady base line throughout which preferably should not need to be checked during the run

6 It should indicate changes of flow instantaneously The recording of mean and pulsatile flow is desirable

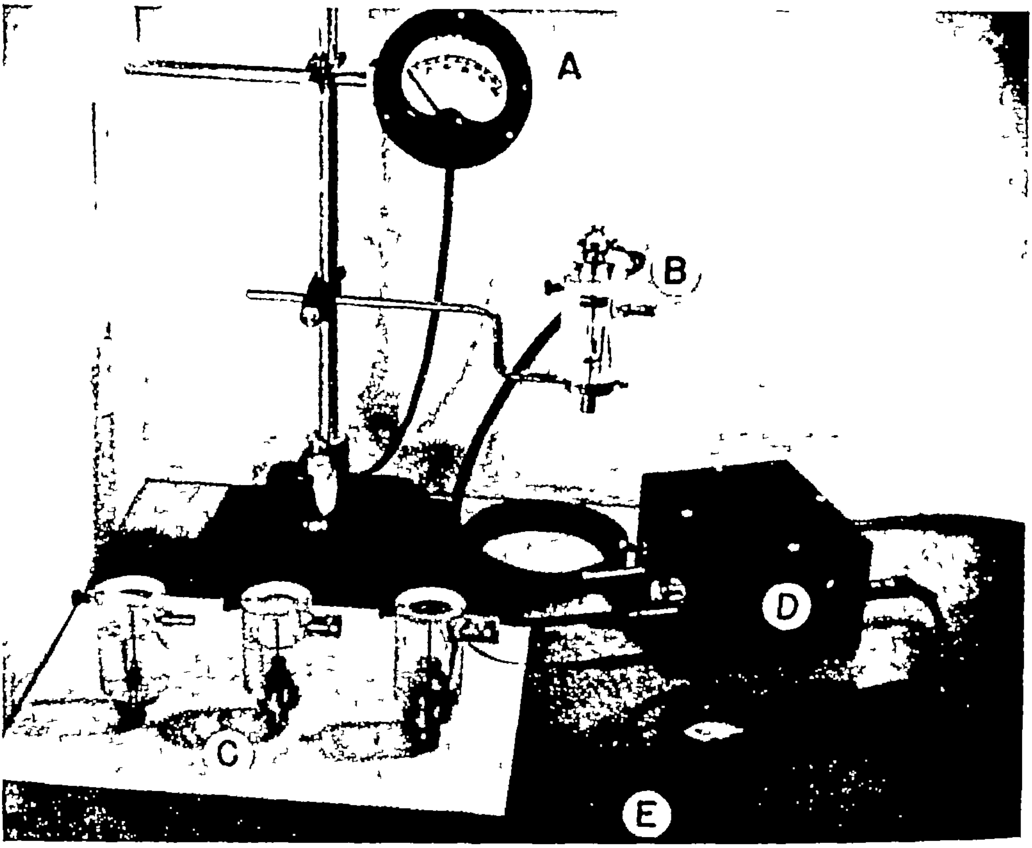


Fig 49 Photograph of apparatus A visual meter, B rotameter, C interchangeable metering chambers accommodating different flow ranges, D control box, E recording mirror galvanometer Reproduced from Shipley, R E, and Wilson, C An improved recording rotameter *Proc Soc Exper Biol & Med* 78 724, 1951

be measured, they provide a further valuable check on the equilibrium of the blood volume in the pump

Calibration of the pump to record flow may be inaccurate unless performed against the expected pressure head

NEED FOR A FLOW METER

(a) It provides a continuous indication of the flow throughout the perfusion and allows instant recognition of alterations in flow rate

(b) Alterations in flow rate may be due not only to physiological changes in the patient but also to mechanical faults in the machine which, however well designed and tested, is still fallible

(c) It provides a cross check on the other physiological meas-

urements being recorded, in particular the venous and arterial pressures as changes in one will always be reflected to some degree in the other two

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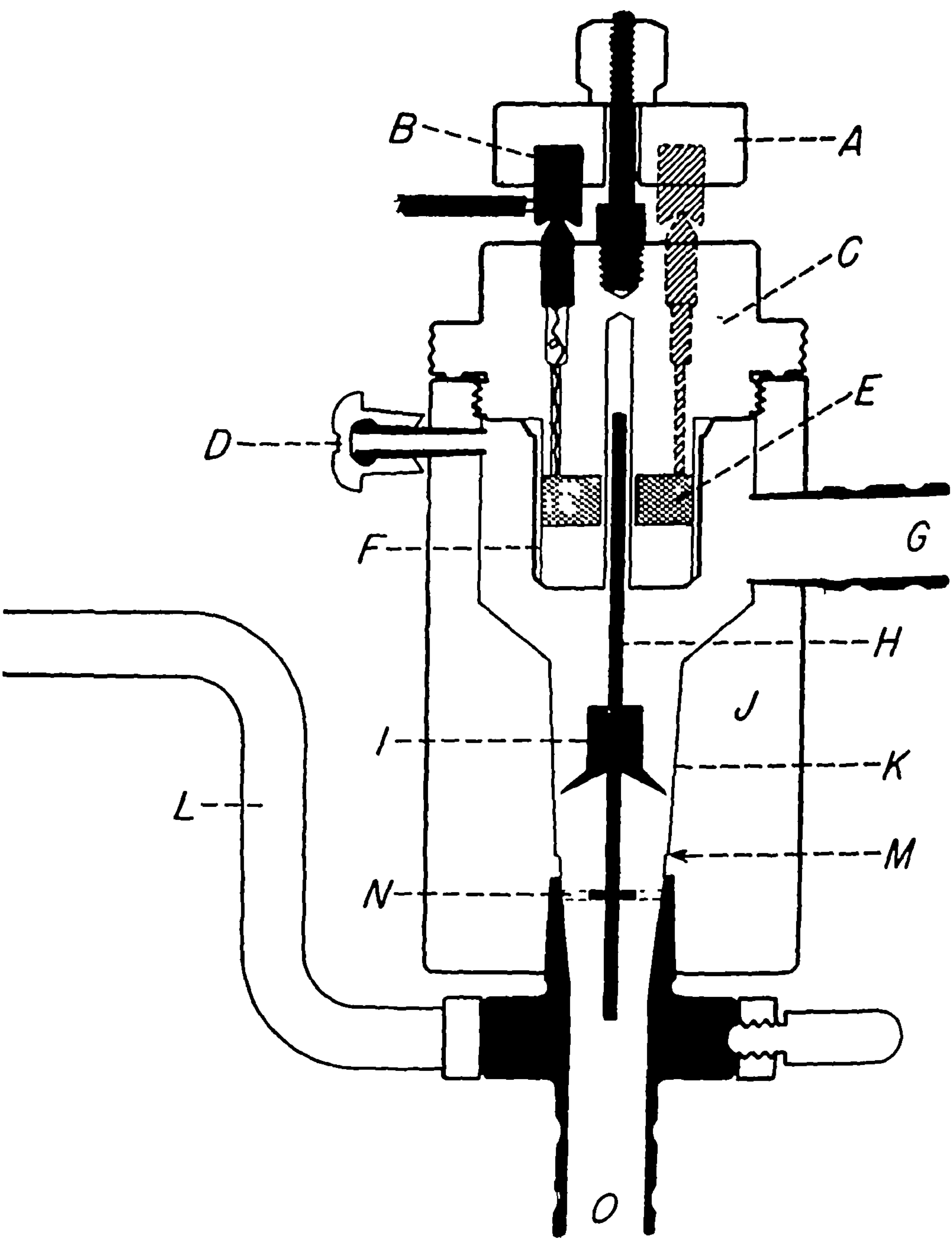


FIG 50 Full-scale sectional view of 0-400 cc/min rotameter constructed of Lucite or Plexiglass with silver plated brass fittings except where otherwise noted A contact holder, B one of 3 contacts communicating with the 2 terminals and common connection of detecting coil and balancing (non-inductive) coil, C detecting assembly, D rubber cap through which air may be removed during filling, E detecting and balancing coils sealed in wax, F protecting sleeve, G outflow spout, H annealed soft iron silver plated float wire, 0 051 inch diameter, I brass float disc Float is shown in position it would occupy in middle of flow range Float is 15 32 inch above float rest when at top of flow range J detachable metering chamber, K metering portion, bored with 0 080 inch per inch taper, L rotameter support, M float rest at zero flow, N float guide, O inflow spout Reproduced from Shipley, R E , and Wilson, C

7 It should be stable in the physiological ranges of tempera ture employed

8 If possible it should be independent of viscosity or density changes

9 It should be able to work in flows at varying pressures i e venous and arterial

10 It should be easily cleaned

TYPES OF FLOW METERS

There are eight main types of flow meters in use and I shall discuss them individually Most of these are used in physiological experiments on animal preparations only but as heart lung ma chines are by necessity extracorporeal the inclusion of a flow meter in the circuit is not difficult

Rotameter

This consists basically of a float of varying shape which is pushed up by the force of the fluid flowing up a tapered tube which contains the float (Fig 49 59)

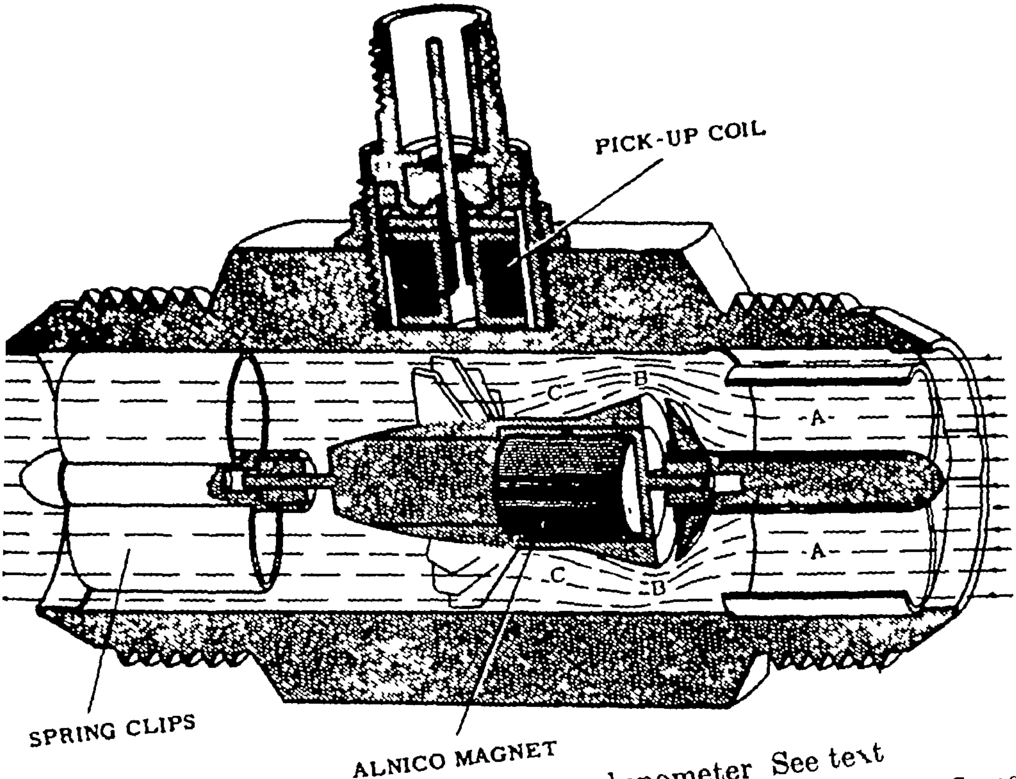
The simplest types can be seen in most anaesthetic machines and are calibrated against a scale on the wall of the float chamber

The more accurate and modern instruments such as that de signed by Shipley and Wilson 1951 [1] depend on a float which is displaced vertically in proportion to the rate of flow and its posi tion detected electromagnetically The rate of flow can be re corded on a micro ammeter for direct reading or through a record ing galvanometer for producing a permanent record

Rotameters can be produced for any flow and their most de sirable characteristic is their simplicity Although I personally have not used them in pumps I have found them efficient in other fields

The disadvantages of rotameters are first, that in general they must be mounted vertically secondly that their calibration curves vary with altering viscosity and thirdly that the float may get adherent particles which alters the calibration

The ball pushed up an inclined plane as used by Senning and his co-workers is a clinical application of this type



The Potter Electroturbinometer See text

Fig 51A The Potter Electroturbinometer See text, Reproduced from Sarnoff, S J, and Berglund, E The Potter Electroturbinometer *Circulation Research*, 1 331, 1953

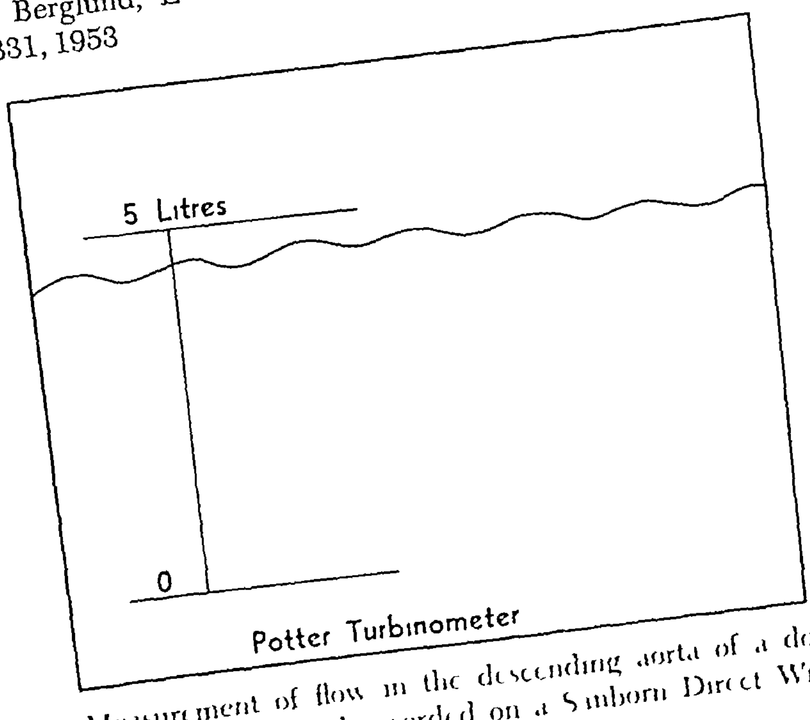


Fig 51B Measurement of flow in the descending aorta of a dog using a Potter turbinometer and recorded on a Sanborn Direct Writer

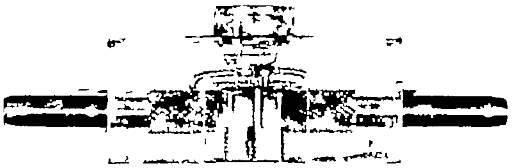


FIG 52 Flow meter head used by McMillan lateral view

Direct Action

This is simply the interposition of something such as a bristle into the flow path and the degree of bending of the bristle is proportional to the flow and can be calibrated and recorded

Its advantage is its simplicity but it is liable to the same troubles as the rotameter and is not so good for recording pulsatile flow

Venturi or Orifice Plate with Differential Pressure Manometers

The physics of the venturi system are beyond the scope of this discussion but the basic principle is the constriction of the flow tube to produce pressure variations in it which can be measured and calibrated, and which alter with varying flows

The advantages of these methods are that they can be used in any position and can have remote indication

This is one of the more promising types but as yet I am not aware of one being used in this field.

The main disadvantage is that the bore of the tube must be narrowed Although this may be insignificant the Pitot holes may get blocked by a clot and spoil the reading and again viscosity or density changes affect the calibration

The electronics are complicated in this machine

Turbinometer

The principle of this machine is that a small turbine or propeller in the bore of the flow tube is rotated by the current In the turbine is a magnet which induces a recordable signal in an

adjacent coil This signal can be traced on any suitable recording apparatus by means of electronic intermediary systems

The Potter Turbinometer which was adapted and developed by Sarnoff, 1953,[2] in this country is a good example and a good physiological instrument in practice, from my experience it is satisfactory in use It is almost independent of viscosity and can be used in any position, and it will record pulsatile and mean flow and has a steady base line over long periods What is recorded is not the E M F generated by the magnet but the number of rotations of the turbine magnet per unit time The advantage of this design of turbine is that all bearings are eliminated and a much steadier calibration is obtained Some pressure drop across the turbine occurs which may be a disadvantage at high flows It has not been used on man (Fig 51A, B)

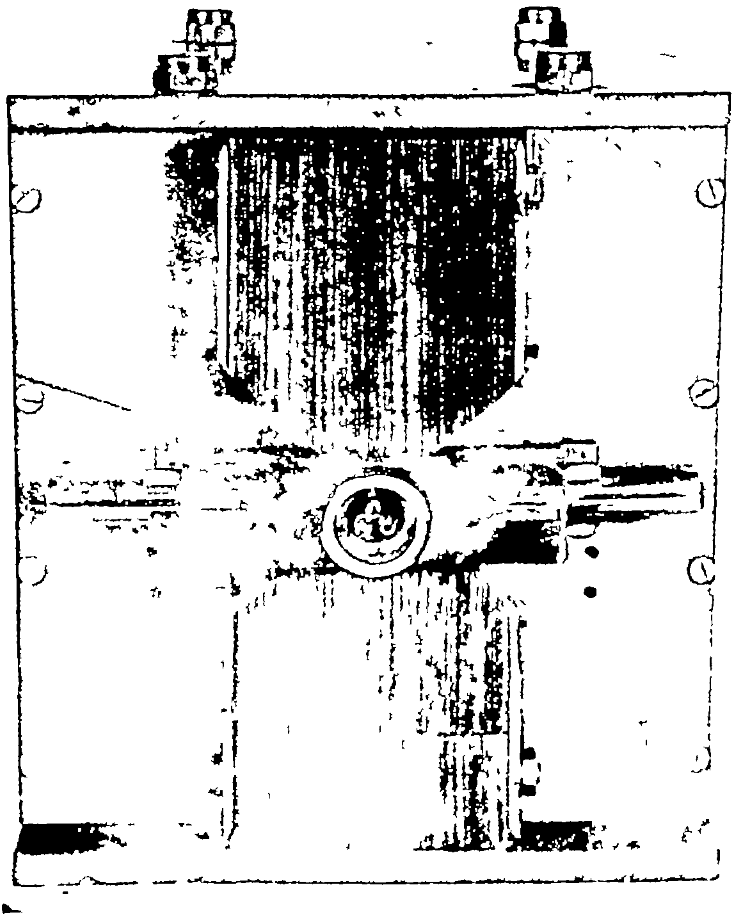


Fig 53 Flow meter head between magnets

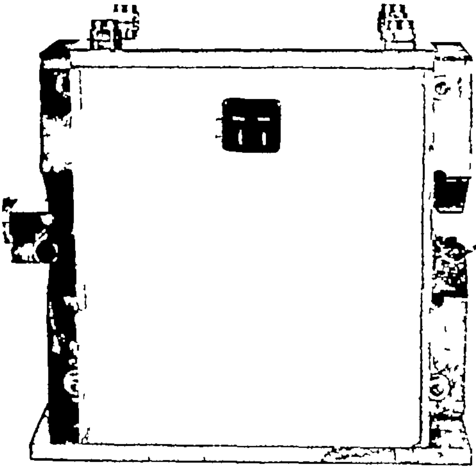


FIG 54 Flow meter head in position between magnets showing twin flow meter positions

Ultrasonic-Doppler Effect

I understand this type is being developed in several places but do not yet know of its use in this field

Electro-Magnetic Induction

This is the type we ourselves use and our own model is now giving reliable results after initial teething troubles (Figs 52, 53 54 55)

The principle is that if a fluid in a tube containing electrolytes passes through a magnetic field, a potential difference will be generated at right angles to that field. The potential difference will be proportional to the velocity of flow and hence after amplification it may operate a recorder or meter calibrated in flow volume

Our machine is modified and developed from that described by Kolin, 1945.[3] But unlike his design, by the use of an alternating magnetic flux, polarization of the electrodes is reduced and so the flow meter is more stable. Its advantages are that it is independent of viscosity and has no restriction of lumen or of any mechanism in the flow path. It is strongly made and easily cleaned; it is not affected by temperature.

Its main disadvantage is its complex electronics which, if not maintained by experts, can lead to zero shifts and other calibration troubles.

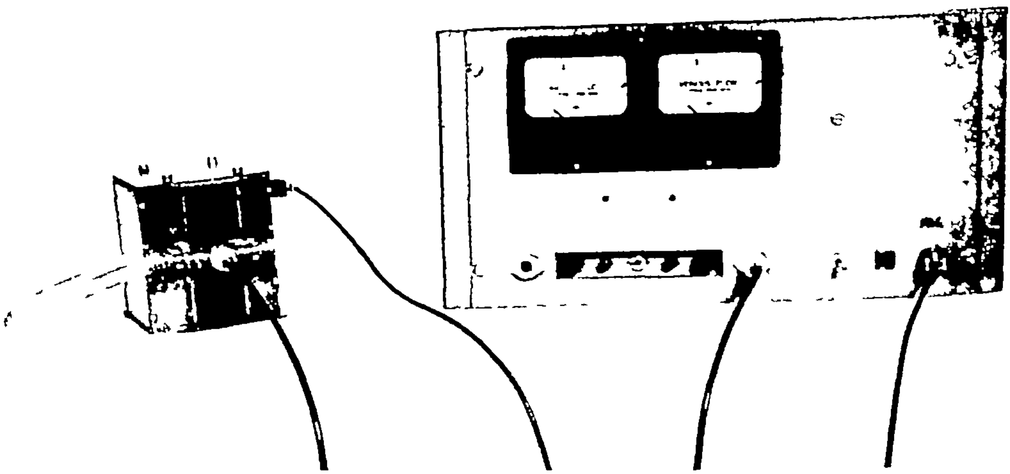


FIG. 55. View of whole flow meter ready for use.

Constant Stroke Volume Pumps

This is not a flow meter but a substitute and is a widely used method of calibrating flow.

In machines which have a fixed stroke volume, flow rate is determined by the number of pump strokes per minute. Thus calibration of flow setting "in vitro" before the pump is connected to the patient should be sufficient.

In addition calibration of other types of pump from previously prepared curves ("in vitro") is a common method.

CONCLUDING REMARKS

Many if not all of us are engaged in trying to develop a satisfactory machine, and it may be that when this end has been

reached and the control of flow is perfect a flow meter may become redundant In the future it may be classed as a physiological instrument only

Physiological measurements are vital in the development stage but many may be able to be eliminated as time goes by Simplicity is as desirable in this field as it is in other branches of surgery

Again in experimental work a really good but perhaps complicated electronic flow meter may be desirable and acceptable in order to define the parameters but in clinical practice the instrument should be simple strong and easy to read

It is desirable to meter both input and output if possible and eventually flow meters in the animal to provide information of perfusion rates of different organs may be of experimental interest

Finally in some of our own work on right sided perfusion of the heart where we require a partial perfusion into the pulmonary artery accurate measurement of flow is vital, and this field with its clinical applications to cor pulmonale which we amongst others are investigating is another example of the heart lung machine s uses

REFERENCES

1 Shipley R. E and Wilson, C An improved recording rotameter *Proc Sec Exp Biol and Med* 78 724, 1951

2. Sarnoff S J and Berglund, E The Potter electroturbinometer *Circulation Research* *1* 331 1953

3 Kolin, A Alternating field induction flow meter of high sensitivity *Review of Scientific Instruments* *16* 109 1945

I would like to thank Mr P R. Styles of St. Thomas s Hospital for the design and construction of the electromagnetic flow meter described.

I would also like to thank Dr S J Sarnoff and Dr R. E. Shipley for permission to use diagrams from their articles on flow meters.

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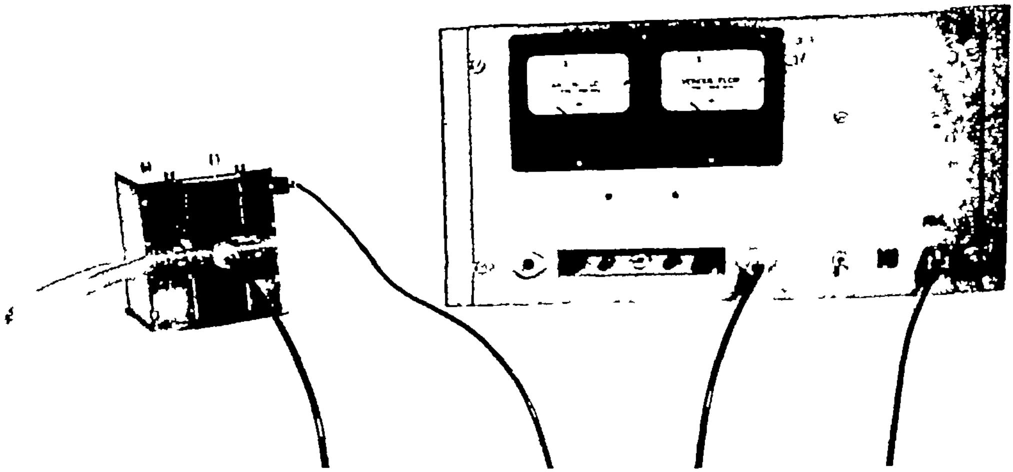


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CONCLUDING REMARKS

Many if not all of us are engaged in trying to develop a satisfactory machine, and it may be that when this end has been

indicates perhaps that the problem of perfusion rate is not solved. There is no doubt that perfusion rate is a function of temperature. I am going to present opinions* concerning the perfusion rate requirements at normal body temperatures. The term "optimum" is used since overperfusion causes unnecessary damage to the patient by virtue of its increased damage to blood. Since we have just recently started perfusion of patients (survival 9 out of 11), these views are based largely on perfusions of about 600 dogs.

Since the apparatus used to study perfusion problems probably has a bearing on the conclusions reached, I would like briefly to describe our perfusion apparatus and its measuring instruments.

The principle of the blood gas exchange system used, namely, bubbling followed by defoaming on a silicone surface, was first described in 1950.[1,2] The pump used, namely, an electrically controlled oxygen piston, was reported in 1952.[3] The original machine required considerable experience and skill to run, but it was entirely capable of providing proper oxygenation, carbon dioxide removal, and flow rate.[4-8] Subsequent modifications made in 1953[9] have made it easier to run and at the same time made it possible to control and monitor the main variables over a wide range. We can control pumping rate to ±3 per cent, pH to ±0.04, temperature to ±0.5°C, and oxygen tension from 90 to 580 mm. Carbon dioxide can, if desired, be retained or flushed out.

Figure 56 is a photograph of the smallest of three sizes of apparatus of similar design in use in Cincinnati, experimentally and clinically. It has a blood volume of 700 cc. and an output of 1.3 liters per minute. It can be assembled in about 30 minutes and can be autoclaved after assembly. Reading from right to left are seen bubbler, defoamer, pump and monitor chambers. Figure 57 shows a close up of the monitor chamber with provision for holding pH electrodes, an oxygen tension electrode[10-12] and a thermistor temperature probe.[13] Provision is made for continuous recording of pH and oxygen tension.

In order to illustrate the control possible, Figure 58 represents

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* These opinions are based upon the results of experiments conducted with Drs. S. Kaplan, E. Matthews and K. Edwards.

OPTIMAL FLOW RATE IN PERFUSION*

By

LELAND C. CLARK, JR., PH.D.

ALTHOUGH the technic of perfusion of living tissue is about one-hundred years old, and has contributed greatly to knowledge in physiology and biochemistry, much of the science of perfusion has developed during the past decade. The major impetus for this development was the need for a means to support the circulation of patients for approximately one hour during open intracardiac surgery. The clinical need for perfusions lasting many hours, or many days, may provide the stimulus for further development.

The greater part of the experimental research, conducted in many laboratories, has consisted of perfusion of the dog with the circulation completely shunted to the apparatus by cannulae tied into the venae cavae through a thoracotomy. The almost universal criterion of a successful perfusion has been the survival of the animal, preferably for a period of several weeks. This criterion has been of great value since surgeons, cardiologists, physiologists, machine designers and machine operators have learned enough to bring us to the present rewarding stage of advance. Solution of the many problems involving heparinization, cannulations, cleanliness, sterility, venous pressures, blood volumes, surface treatments such as siliconing, blood filtration, temperature control, hemolysis, machine design, and so on, often tend, however, to obscure the main purpose of the perfusion namely, to meet the oxygen requirement of the animal and to quantitatively dispose of the resultant carbon dioxide. The observation that many perfusion groups still have a hypothermic annex,

* This work was supported in part by grants from the American Heart Association and the U S P H

indicates perhaps that the problem of perfusion rate is not solved There is no doubt that perfusion rate is a function of temperature I am going to present opinions* concerning the perfusion rate requirements at normal body temperatures The term "optimum" is used since overperfusion causes unnecessary damage to the patient by virtue of its increased damage to blood Since we have just recently started perfusion of patients (survival 9 out of 11) these views are based largely on perfusions of about 600 dogs

Since the apparatus used to study perfusion problems probably has a bearing on the conclusions reached I would like briefly to describe our perfusion apparatus and its measuring instruments

The principle of the blood gas exchange system used namely bubbling followed by defoaming on a silicone surface was first described in 1950[1,2] The pump used namely an electrically controlled oxygen piston was reported in 1952[3] The original machine required considerable experience and skill to run but it was entirely capable of providing proper oxygenation, carbon dioxide removal, and flow rate[4-8] Subsequent modifications made in 1953[9] have made it easier to run and at the same time made it possible to control and monitor the main variables over a wide range We can control pumping rate to ± 3 per cent pH to ± 0.04 temperature to ± 0.5 C and oxygen tension from 90 to 580 mm Carbon dioxide can if desired be retained or flushed out

Figure 56 is a photograph of the smallest of three sizes of apparatus of similar design in use in Cincinnati, experimentally and clinically It has a blood volume of 700 cc and an output of 1.3 liters per minute It can be assembled in about 30 minutes and can be autoclaved after assembly Reading from right to left are seen bubbler defoamer pump and monitor chambers Figure 57 shows a close up of the monitor chamber with provision for holding pH electrodes an oxygen tension electrode[10-12] and a thermistor temperature probe[1] Provision is made for continuous recording of pH and oxygen tension

In order to illustrate the control possible Figure 58 represents

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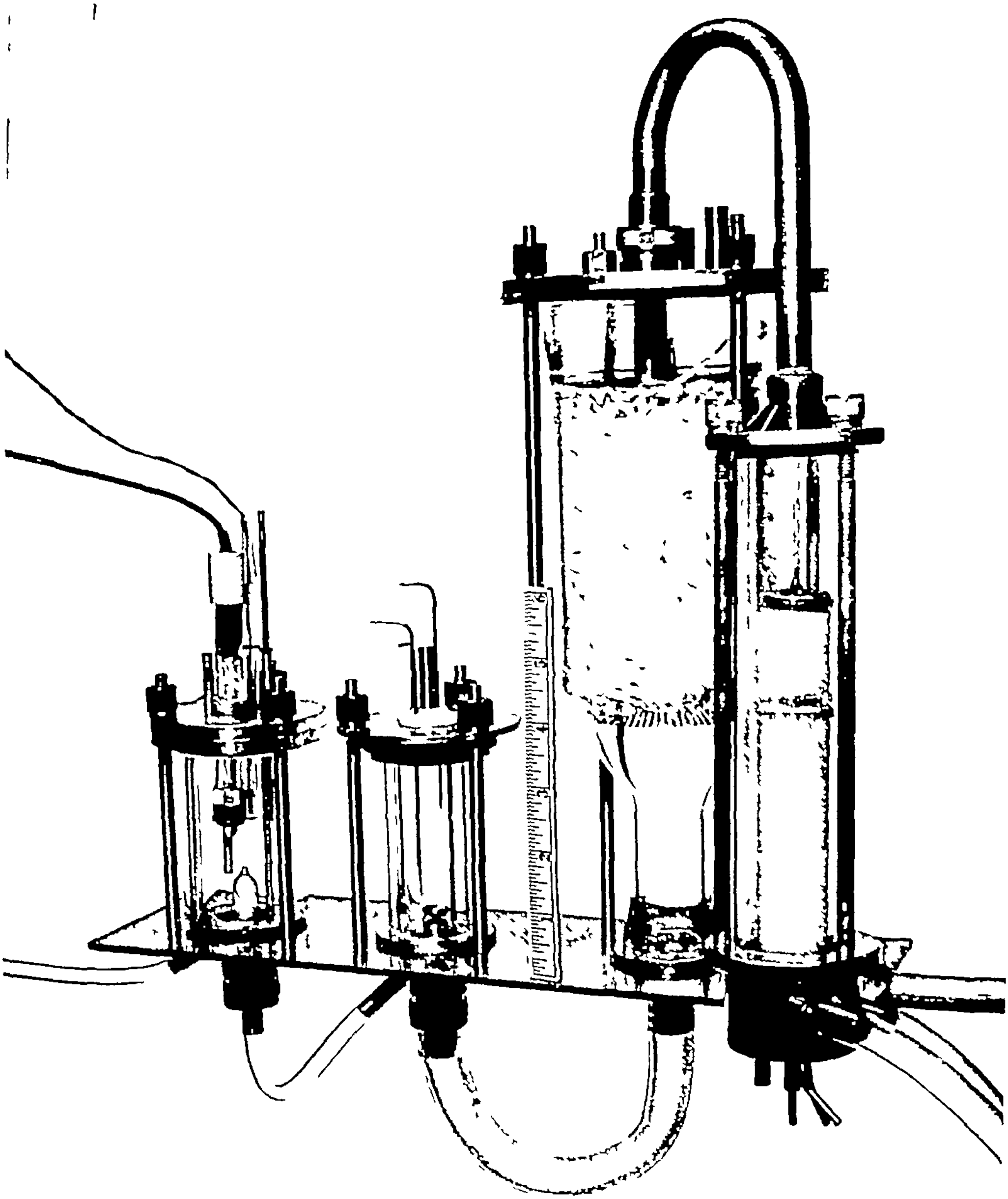


FIG 56 Apparatus designed for perfusion of infants The cylinder on the right contains a medium and coarse porosity bubbler with separate oxygen inlets, the large defoaming chamber, packed with polymethyl-siloxane-coated Teflon shreds, is held under 90 mm Hg suction, the pumping chamber to the left has a stroke volume adjustable from 10 to 40 cc , the unit on the far left holds the pH, pO. and temperature probes The unit is made of glass, stainless steel, and Teflon, can be autoclaved after assembly, has a blood volume of 700 cc and an output of 1 2 liters per minute

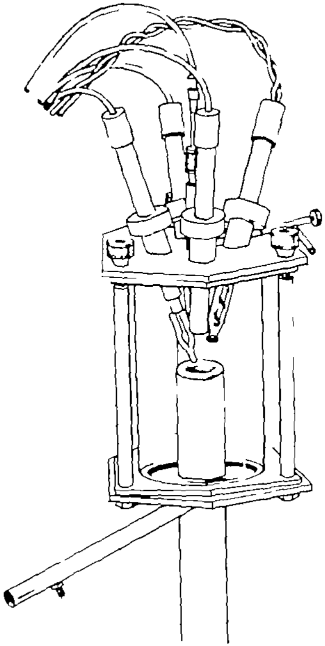


Fig 57 The monitor chamber This unit can hold four conventional-size (1 2" × 4") electrodes and a thermometer probe Usu ally it is equipped with two pH electrodes and a pO electrode while elec trodes under development are held in the fourth space A small volume of oxygen is trapped above the blood to "buffer" the stroke of the pump and provide gas to equilibrate the pressure of electrolyte in the pH reference elec trode

the mean blood pH and the extreme range of pH on ten consecu tive patients Ninety per cent of the values fall within a pH of 7 40 ± 0 05 Although the CO tension of the initial incoming blood from the patient can be rapidly altered if it is too high or too low we prefer to slowly adjust it by adjusting the pH towards 7 40 This accounts for the shape of the curve The arterial oxy gen tension in the cases represented in Figure 58 was held be tween 560 and 580 mm

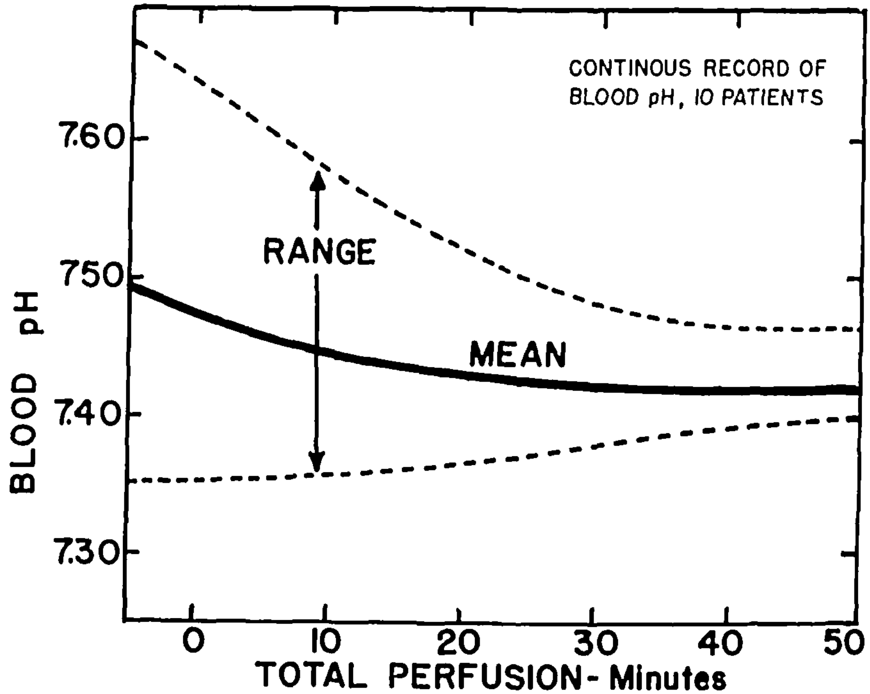


FIG 58 Control of blood pH in ten consecutive patients The graph shows the mean and extreme range The pH is monitored continuously at 37°C

Oxygen transfer, being largely dependent on surface area, is a function of the number of small bubbles CO_2 tension, being largely dependent on the volume of the gas used in bubbling, or in other words, on the CO_2 tension in the bubble itself, is a function of the number of large bubbles

There are many ways to regulate the relative number of small and large bubbles The three which have been used in our laboratory are

1 As oxygen flow through a porous material in contact with blood is increased, the amount of gas emerging as large bubbles increases with a slight decrease in the amount of small bubbles

2 As the interfacial tension between the blood and the porous material is lowered, the size of the emerging bubbles, at a given gas flow is, greatly decreased This is readily accomplished by minute amounts of non-toxic, non-hemolytic surface-active agents, such as Triton

3 Coarse and fine porosity bubblers can be used with separate oxygen feed lines Because less experience is necessary, and because it is more easily reproducible, this third method has been

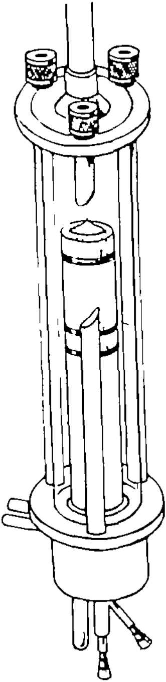


FIG 59 The bubbler unit The outer cylinder is glass (for autoclaving) or Lucite (for animal work) The top of the center cylinder is a one-inch long section of Corning s "coarse" sintered glass the lower part is a four inch section of Corning s "medium" or "fine" porosity sintered glass Separate oxygen flow is provided to each porosity bubbler Venous inlets (vena cava and "coronary venous") are provided at the bottom

used in our laboratory since 1953 A sketch of the bubbler unit used is shown in Figure 59

Aside from this it must be mentioned that small bubbles cause more hemolysis than large bubbles [4] and that large bubbles denature proteins as revealed by bubbling urease and catalase solutions [18] Disturbance to protein solutions may result whenever

such solutions have a gas-liquid interface (for example see activation of lipolysis in milk, by agitation or foaming[16] or denaturation of albumin in the absence of air as compared to the presence of air in silicone-lined bottles[17]). The development of membrane oxygenators will eliminate this problem.

The Gollan oxygenator[18] represents the fine bubble end of the scale and the DeWall oxygenator[19] the other end of the scale.

In order to obtain oxygen requirements to serve as a means of computing perfusion rate, basal metabolic rate determinations on children were collected[20-26] and used to plot a curve related to weight. This curve is shown in Figure 60.

The equation* for perfusion rate containing the essential variables is

$$P = \frac{7.46\ WR}{H\ (A\text{-}V)} + C$$

where

P = Perfusion rate (liters per minute)
7.46 = A constant due to the units chosen
W = Body weight (kg.)
R = Oxygen requirement (cc./kg./min.)
H = Hemoglobin (gm. per cent)
A = Arterial saturation (per cent)
V = Venous saturation (per cent)
C = Coronary and bronchial venous blood

For the purpose of preparing a guide to perfusion rates, we have chosen a venous saturation of 50 per cent as representing a compromise after consideration of the following: the normal

---

* This is an expression of the Fick principle where hemoglobin and per cent venous saturation are substituted for the usual denominator thus:

Perfusion rate = oxygen needed divided by the oxygen supplied in a given volume of blood.

Oxygen needed per minute = requirement (from BMR). Requirement here is derived from Figure 60 as cc./kg./min. multiplied by the weight in kg.

Oxygen supplied per minute = Hemoglobin content, as gm. per 100 cc. multiplied by the oxygen content of a gm. of hemoglobin (1.34 cc.) multiplied by the A-V difference.

Therefore

P = WR divided by 1.34 H (A-V) or, moving the constant to the numerator,

P = 7.46 WR divided by H (A-V)

C, the so-called 'coronary venous' blood may reach very high values in sinus rhythm or fibrillating hearts. In these cases, we usually increase the flow by one-half of C.

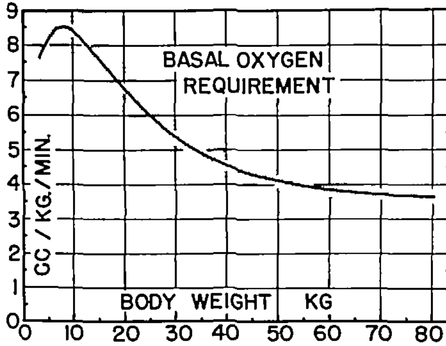


FIG 60 Basal metabolic rate vs body weight. The shaded portion represents approximately the range which would include 80 per cent of the normal population

basal venous saturation the fact that the anesthesia probably lowers the oxygen requirement that oxygen needs of individuals vary one from another and that during the course of a surgical procedure oxygen requirements may vary from minute to minute Because the hemoglobin content of perfusion blood varies and because it is such an important variable it is taken into account in deciding a given perfusion rate We consider the extra oxygen carried at a pO_2 of 580 mm as roughly equivalent to one gram of hemoglobin. Since oxygenation of tissues from the venous side is a demonstrable phenomenon,[27, 28] it is vital to not only maintain normal venous pressures but also adequate venous pO_2 and pCO_2

Figure 61 shows the family of curves relating perfusion rate and hemoglobin to body size *

Charts relating perfusion rate to either surface area or body weight are available by writing to Leland C. Clark Jr Fels Research Institute Antioch College Yellow Springs, Ohio It should be noted that the surface area—perfusion rate is also curvilinear and that until perfusion rate standards can be recommended by an appropriate committee the relationship based on weight may perhaps, be more reliable and convenient.

such solutions have a gas-liquid interface (for example see activation of lipolysis in milk, by agitation or foaming[16] or denaturation of albumin in the absence of air as compared to the presence of air in silicone-lined bottles[17]) The development of membrane oxygenators will eliminate this problem

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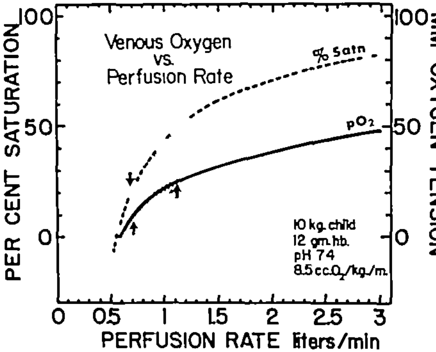
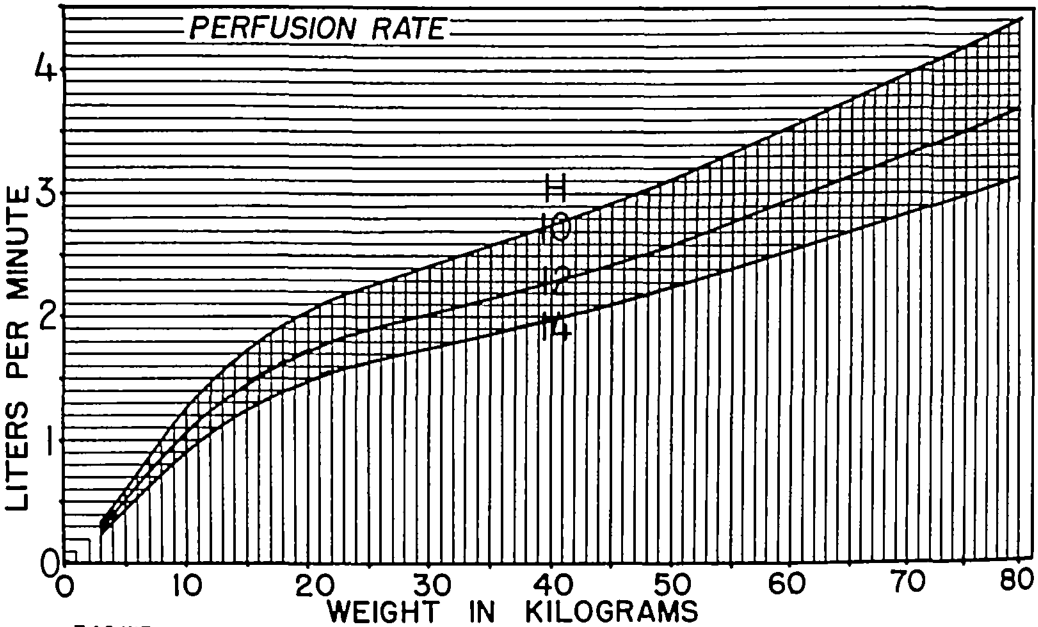


FIG 62 Calculated relationship between venous oxygen and perfusion rate

of the oxygen dissociation curve The two curves illustrate two points that the venous tension plunges toward zero in passing through the critical region represented by slowing the perfusion rate from one liter per minute to 0 6 liter per minute and that a venous pO_2 monitoring device must have high precision to accurately reflect changes in flow rate It seems to me that the factors discussed so far help to explain the finding that when two animals are perfused at the same flow rate expressed merely as cc /kg / min one may survive an hour of perfusion, while the other may not. When attention is paid to the variables mentioned our survival rate in laboratory perfusion of about one hour is 95 per cent."

Our views of the consequences of underperfusion are perhaps best represented by the experiment selected for Figure 63 Here the flow rate was increased stepwise in three 15-minute periods from 25 cc /kg /min to 35 and to 56 The oxygen consumption increased each time the perfusion rate was increased. The most important observation during perfusion was the drop in blood pH encountered during the low flow period an acidemia which



$P = \frac{7.46\ WR}{H(A-V)}$ where P = perfusion rate (l/m), W = body weight (kg), R = oxygen requirement (cc/kg/m), H = hemoglobin (g%), A = arterial satn. (%, assumed 100), V = venous satn. (% assumed, 50) L Clark, Antioch, Yellow Springs, O

FIG 61 Calculation of perfusion rates vs body weight

The perfusion rate requirement rises rapidly between 5 and 20 kg of weight and then slopes off to a rate which becomes progressively less up to 80 kg of weight The importance of knowing the hemoglobin content is readily appreciated from this graph Note that a 10 kg child requires 1100 cc per minute or one-third the requirement of a 70 kg adult Looking at the requirements of infants and young children more closely we can see that the peak requirement is in a 9 kg child (105 cc /kg /min) and that it becomes less (100 cc /kg /min) for a 5 kg child and less (97 cc /kg /min) for a 15 kg child It seems remarkable that a 9 kg baby can meet his basal oxygen requirements and even more remarkable that a few babies at this age have the reserve cardiac output to walk They are, at rest, exchanging their blood volume more than 1 5 times per minute Perhaps special care should be taken to insure a high post-operative hemoglobin in patients between 5 and 20 kg in weight

If one assumes, for the moment, that the body is a uniform capillary network, having a steady oxygen consumption, Figure 62 shows how venous oxygen varies with perfusion rate The shape of the lower curve for venous pO_2 is, of course, due to the shape

SUMMARY

It is suggested that optimum perfusion rate be based upon basal oxygen requirement 50 per cent venous saturation and the hemoglobin content of the perfused blood Further research is necessary in order to accurately adjust perfusion rate to the needs of the individual patient during the course of long perfusions

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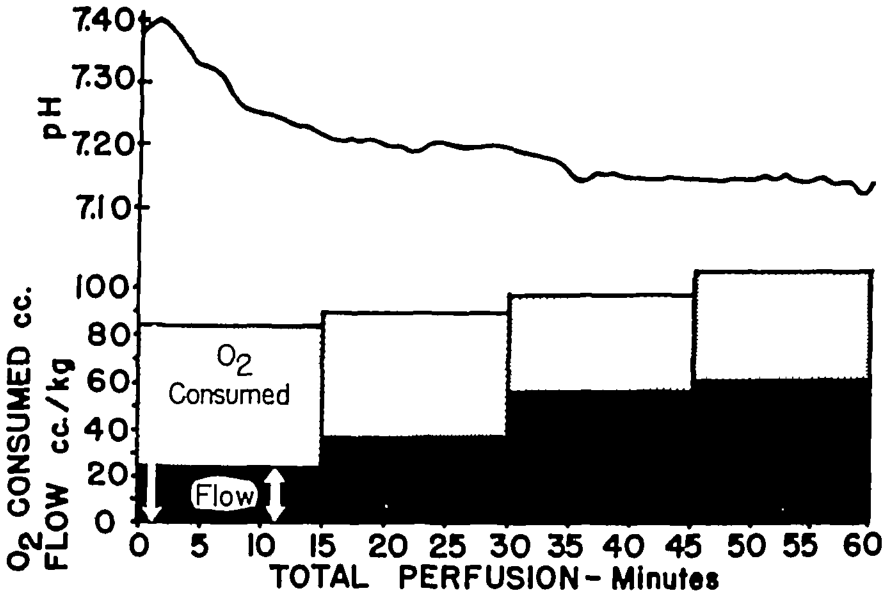


FIG 63 Drop in blood pH associated with low perfusion rate, uncorrectable by increasing the perfusion rate

could not be corrected by increasing perfusion rate or by increasing ventilation rate (amount of large bubbles) Subsequent analysis revealed normal pCO_2 values throughout This metabolic acidosis was followed by a post-operative course characterized by excessive oozing from wounds and a slow recovery of reflexes After replacing blood losses of 800 cc with fresh whole blood, the animal continued to bleed throughout the night and finally died On autopsy the following morning 1100 cc of blood was found in the pleural cavity

There must be another equation where time is multiplied by oxygen debt per minute to yield capillary damage Perhaps this can be determined empirically by measurements of venous oxygen during perfusions Abrupt increases in capillary permeability have been reported in hypoxic perfusions of isolated organs [30]

Lastly, our data reveal that oxygen utilization may vary by a factor of 1 8 during a one-hour perfusion in a Nembutal-anesthetized dog This has strengthened our opinion that in long perfusions one must be generous with perfusion rate or must have sensitive indicators to monitor venous oxygen content and arterial blood pH

SUMMARY

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STUDIES ON VARYING RATES OF PERFUSION FOR INTRACARDIAC OPERATIONS USING THE HELIX-RESERVOIR OXYGENATOR

By

RICHARD L. VARCO, M.D., CHRISTIAAN BARNARD, M.D.,
RICHARD A. DEWALL, M.D., *and*
C. WALTON LILLEHEI, M.D.

PERFUSION rates somewhat below the resting cardiac output have been used in virtually all cardio-pulmonary by-pass procedures carried out at the University of Minnesota Hospitals to date. In the beginning, this concept was a necessity inasmuch as we were obligated to develop successful perfusion techniques involving low flows before higher flows could be successfully managed. Experience, knowledge, and refinements in perfusion equipment and technique have now reached the point where there are no limitations upon pump or oxygenator capacities and the problem has become one of determining what is optimal rather than what is possible. This problem has been investigated by analysis of results of several hundred experimental and clinical perfusions respectively. Our interest was attracted to the concept of pumping sub-basilar flows, during the necessary interval of cardiopulmonary by-pass, by the work of Andreason and Watson.[1] They observed that a dog heart would tolerate thirty minutes of venous inflow stasis save for that amount permitted to enter the right auricle via the unobstructed azygous vein. In other words, with both the superior and inferior vena cavae clamped in such a fashion as to permit only the azygos tributary to remain open, this limited volume entering was yet sufficient to nourish the heart and maintain viability in the other essential structures for an interval as long as thirty minutes. This idea was studied in considerable detail and confirmed by the extensive experimental observations of Cohen.[2] He repeatedly

demonstrated the validity of this principle in his studies on dogs Subsequent experiments also carried out in the surgical research laboratories of the University of Minnesota ascertained that this reduced volume of blood could be provided safely by a donor animal without prejudicing the latter animal s cardiovascular equilibrium Furthermore with this time interval of thirty min utes available for intracardiac surgery it appeared extremely likely from our study of and simulated operations on autopsy specimens that a wide variety of intracardiac lesions could be curatively treated. Accordingly on March 26 1954 and using controlled cross circulation the principle of perfusion with a flow below that of the resting cardiac output was first tested clinically This initial case was successfully treated Reaffirmations of the validity of this concept were secured in the subsequent forty five cases operated upon using this means Once the helix reservoir[3] bubble-type oxygenator was sufficiently well developed in the laboratory and having been tested there shown to be a suitable substitute for controlled cross circulation it appeared reasonable to accumu late more clinical experience with perfusions at various levels and then analyze the accomplishment and performance under these varying conditions The results of certain of these studies will be detailed in this paper

Beyond the initial advantage of increased safety to the donor in those instances where controlled cross circulation was used there are yet other advantages accruing through the use of per fusion rates subbasal to the resting cardiac output First, with all existing pumping devices now in use it is certain that additional trauma from impact greater likelihood of turbulence and other internal forces applied to the stream is present the greater the volume moved per unit time Secondly the problems of cannula tion are enhanced when large flows must be pumped Thirdly with increased perfusion rates the problem of managing the more voluminous coronary sinus bronchial artery return grows more troublesome Particularly in the instance of tetralogy of Fallot patients these quantities gushing into the heart can add con siderably to the technical problems of the repair and are often associated with an increased blood loss during the operation unless this abundant return is successfully restored to the pump

ing circuit Arresting the heart under these circumstances is not a cure-all It carries intrinsic disadvantages which need to be appreciated and evaluated against the gains in exposure and a drier field, whenever this technique is electively added to the operative procedure Whereas little has been written about the appearance of diffuse and focal areas of myocardial necrosis, we have noted this occurrence in patients undergoing cardiac arrest Even though these individuals establish a regular rhythm post perfusion, ultimately they have succumbed We have reason to believe that similar experiences have been encountered by others using the technique of potassium citrate induced arrest Moreover, the incidence of permanent heart block is unquestionably increased in those patients undergoing cardiac arrest Upon nine occasions we have noted at the moment of placement of a specific suture the development of a complete atrio-ventricular dissociation in the rhythm Following removal of this offending stitch, ultimately always (and often abruptly) a normal sinus action has been restored Clearly, this sequence of detection and correction are impossible if the heart has been arrested Finally, in our own experience with several hundred cases of intracardiac surgery the incidence of heart block is twice as great among those persons receiving elective cardiac arrest as it has been in the series in which this was not carried out Although the current management of complete heart block with the use of Isuprel and a pacemaker wire[4,5] is superior to other forms of management, we still believe that complete heart block is a serious complication and a grave defect for any individual to carry through life Also it is pertinent to indicate that in the patient undergoing cardiac arrest who is found to have hitherto unrecognized aortic insufficiency, or in whom this complication is created during the operation, the re-establishment of an effective beat can be extremely difficult or impossible by ordinary means Without recourse to retrograde coronary sinus perfusion, it is quite unlikely that an effective cardiac beat will ever be established The left ventricular fibers are irrevocably stretched beyond their useful length when the aortic clamp is removed and blood under perfusion pressure pours into the inert left chamber Before the citrate is washed from the myocardium fatal damage can be done to the contractile elements

A variety of methods are available for demonstrating the effectiveness and consequences of perfusing patients with flows subbasal to the resting cardiac output For instance the biochemical aspects of this problem and the accomplishments of the oxygenator under these circumstances have been detailed elsewhere [7] Data derived both from animal experiments and from clinical material are shown in Tables I and II In Table I at perfusion rates of from 16 cc /kilo /min to 50 cc kilo min the arterial

TABLE I

ARTIFICIAL OXYGENATOR

Gas Exchange Efficiency at Various Flow Rates
Values at 30 Minutes of Total By-Pass

Perfusion Rate cc /kg	*Oxygen Saturation %*				*Total CO₂ mm /l* †		
	No Dogs	*Arterial*	*Venous*	*A V Diff*	*Arterial*	*Venous*	*A V Diff*
*Pre perfusion Control**	70	98	63	35	18 2	22	3 8
16–20	4	90	15	84	13 3	20 3	7 0
21–25	9	97	22	73	14 0	19 2	5 2
26–30	13	98	27	71	14 4	19 5	5 1
31–35	12	101	34	67	17 0	20 1	3 1
36–40	11	102	37	65	17 2	22 5	5 3
41–45	7	100	40	51	15 4	20 6	5 1
46–50	7	98	54	44	18 0	21 1	3 1

* Samples drawn after chest opened and on mechanical respirator
† Normal Values = Arterial 21–22 Venous 23–24 mm /l

TABLE II

TOTAL CARDIOPULMONARY BY PASS

Utilizing the Artificial Pump-Oxygenator

J L, 38 Years
I V S.D with Pulmonary Hypertension
Perfusion Rate 34 cc /kg
Temperature (R) 100.2 F

Source of Blood Sample	*Patient (Control)*		*Pump (Defect Closed*)*	*Pump (End By-Pass†)*		*Patient (15 Min after)*
	Artery	*Vein*	*Venous*	*Arterial*	*Venous*	*Artery*
pH	7 58	7 43	7 40	7 47	7 40	7 38
Oxygen Content (Vol. %)	—	10 1	9 5	21 4 (98%)	11 8	18 0
CO₂ Content (mm./l.)	21 2	24 5	23 9	18 0	22 7	20 2
Lactic Acid (mg %)	23 6	22 1	23 1	24 7	20 7	29 0

* 13 minutes.
† 19 minutes, plasma hemoglobin = 21 mg %.

ing circuit Arresting the heart under these circumstances is not a cure-all It carries intrinsic disadvantages which need to be appreciated and evaluated against the gains in exposure and a drier field, whenever this technique is electively added to the operative procedure Whereas little has been written about the appearance of diffuse and focal areas of myocardial necrosis, we have noted this occurrence in patients undergoing cardiac arrest Even though these individuals establish a regular rhythm post perfusion, ultimately they have succumbed We have reason to believe that similar experiences have been encountered by others using the technique of potassium citrate induced arrest Moreover, the incidence of permanent heart block is unquestionably increased in those patients undergoing cardiac arrest Upon nine occasions we have noted at the moment of placement of a specific suture the development of a complete atrio-ventricular dissociation in the rhythm Following removal of this offending stitch, ultimately always (and often abruptly) a normal sinus action has been restored Clearly, this sequence of detection and correction are impossible if the heart has been arrested Finally, in our own experience with several hundred cases of intracardiac surgery the incidence of heart block is twice as great among those persons receiving elective cardiac arrest as it has been in the series in which this was not carried out Although the current management of complete heart block with the use of Isuprel and a pacemaker wire[4,5] is superior to other forms of management, we still believe that complete heart block is a serious complication and a grave defect for any individual to carry through life Also it is pertinent to indicate that in the patient undergoing cardiac arrest who is found to have hithertofore unrecognized aortic insufficiency, or in whom this complication is created during the operation, the re-establishment of an effective beat can be extremely difficult or impossible by ordinary means Without recourse to retrograde coronary sinus perfusion, it is quite unlikely that an effective cardiac beat will ever be established The left ventricular fibers are irrevocably stretched beyond their useful length when the aortic clamp is removed and blood under perfusion pressure pours into the inert left chamber Before the citrate is washed from the myocardium fatal damage can be done to the contractile elements

short period of time as seen in Figure 66 a more normal electro encephalographic pattern is restored As this wave sequence once again converts to a less satisfactory state with an over all lower ing of activity (Fig 67) it is possible to improve this as shown in Figure 68 by increasing the input i e perfusion rate a predeter mined amount Once again there is a restoration of a more normal electroencephalographic pattern The final appearance of the early post perfusion tracing is shown in Figures 69 and 70 More over since it is readily possible to prearrange the calibrations for the pump output for several values it is therefore feasible to boost sequentially the volume being perfused judging this need as it is manifest on the constantly monitoring electroencephalo-gram As further corroboration of the effectiveness of so supple-menting the flow during the course of a run it can be shown by direct pressure measurements made through a previously inserted polythene tube in the divided internal mammary artery carried out at the time of the transverse thoracotomy that a corresponding lift appears on the blood pressure tracing simultaneously with each shift to a higher flow value It is a mistake to equate a seemingly adequate pump output with an acceptable cerebral blood flow In at least two circumstances such a judgment can have dire consequences In the case of a patient with an over looked patent ductus arteriosus or an individual with the tet ralogy of Fallot defects and large bronchial collaterals can so effectively bleed off volumes from the ordinarily adequate per fusion flow that a quite insufficient amount eventually reaches the cerebrum the electroencephalogram can become flat. Therefore in the instance of the ductus it is essential to identify this criti cal leak and close it and in the case of the tetralogy patients the perfusion rate must be raised enough to produce a satisfactory electroencephalogram And in fact this degree of monitoring is a highly desirable part of each cardio-pulmonary by pass

To secure yet another evaluation of the consequences and ac complishments of perfusions at flows sub-basal to the resting car diac output the end arterial pH and duration of perfusion for varying rates have been charted in Figures 71 72, and 73A B In each instance the duration of the perfusion has been plotted on the ordinate and the pH along the abscissa Graphs have then

oxygen saturation is uniformly high. Since the venous oxygen saturation at the lower flows is lower, and hence the oxygen extraction ratio is higher, presumably the tissues are thus assisted in meeting their oxygen needs despite the more limited supply of oxygen brought to them Carbon dioxide clearance from the venous blood, as can be seen by reference to these charts, was even effectively cared for at the very lowest flows The demonstrated tendency toward a shift in the pH to the acid side is, therefore, due to the accumulation of acid metabolites The largest of these is lactic acid, and the value for this, together with other relevant data, as secured in a typical case, is shown in Table II In the over-all evaluation of this degree of lactic acid rise, it should be recalled that the anesthetized patient without undergoing a cardio-pulmonary by-pass also develops a mild acidosis, and on this same basis The causes for lactate rise under both circumstances are probably comparable, namely, the failure of soft tissue metabolism to complete the breakdown of carbohydrate to CO_2 and H_2O, probably because of the restraining influence of a relative lack of oxygen on essential enzymatic processes Then, too, general anesthetic agents depress oxygen consumption With the restoration of an adequate circulation in the postoperative period, modest imbalances of this type are promptly corrected within the body so that a normal arterial pH is soon achieved[6]

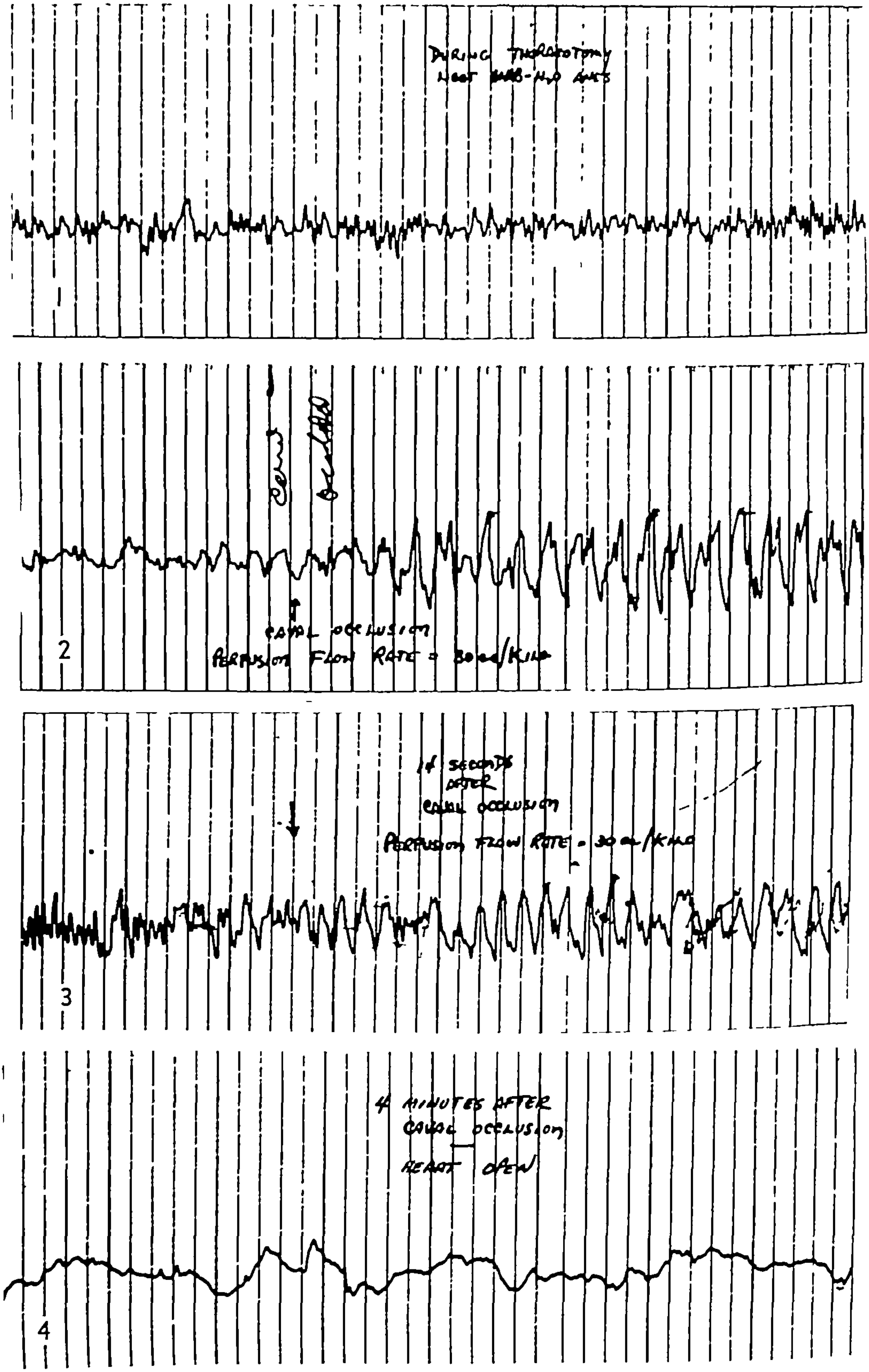
A second way in which to consider the consequences of perfusions at sub-basal flows is to examine the electroencephalographic response under these conditions These tracings have been obtained by the usual methods in more than 200 cases A more detailed description of the findings has been published elsewhere[8] Appropriate segments from a typical tracing are shown in Figures 64 through 70 The usual rapid activity of alpha and beta waves, together with whatever mild suppression has been induced by the light plane of anesthetization brought about in this case by pentothal, a muscle relaxant, and nitrous oxide, is shown in Figure 64 Immediately after inducing inflow stasis (Figure 65) by occluding the caval return to the heart, a change appears in electroencephalographic pattern The slower, deep waves which result are less desirable, and suggest that a period of adaptation is occurring in the cerebral blood flow Within a

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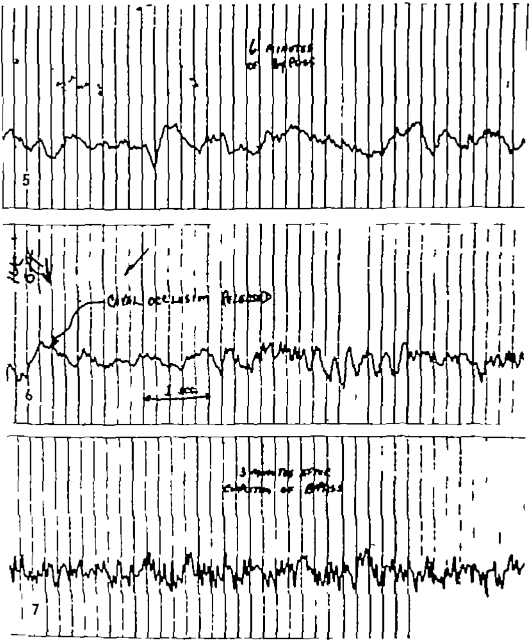
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Figs 64-67 (top to bottom) (Legend on facing page)



Figs 68-70 (top to bottom)

Figs 64-70 Electroencephalographic tracings demonstrating usual findings in a cardio-pulmonary by-pass at a subbasal flow Note changes in electrical activity under varying influences and response toward a more satisfactory pattern after flow has been increased (but remains well below resting cardiac output) (Figure 68 Figure 69) Final tracing (Figure 70) is virtually a normal one

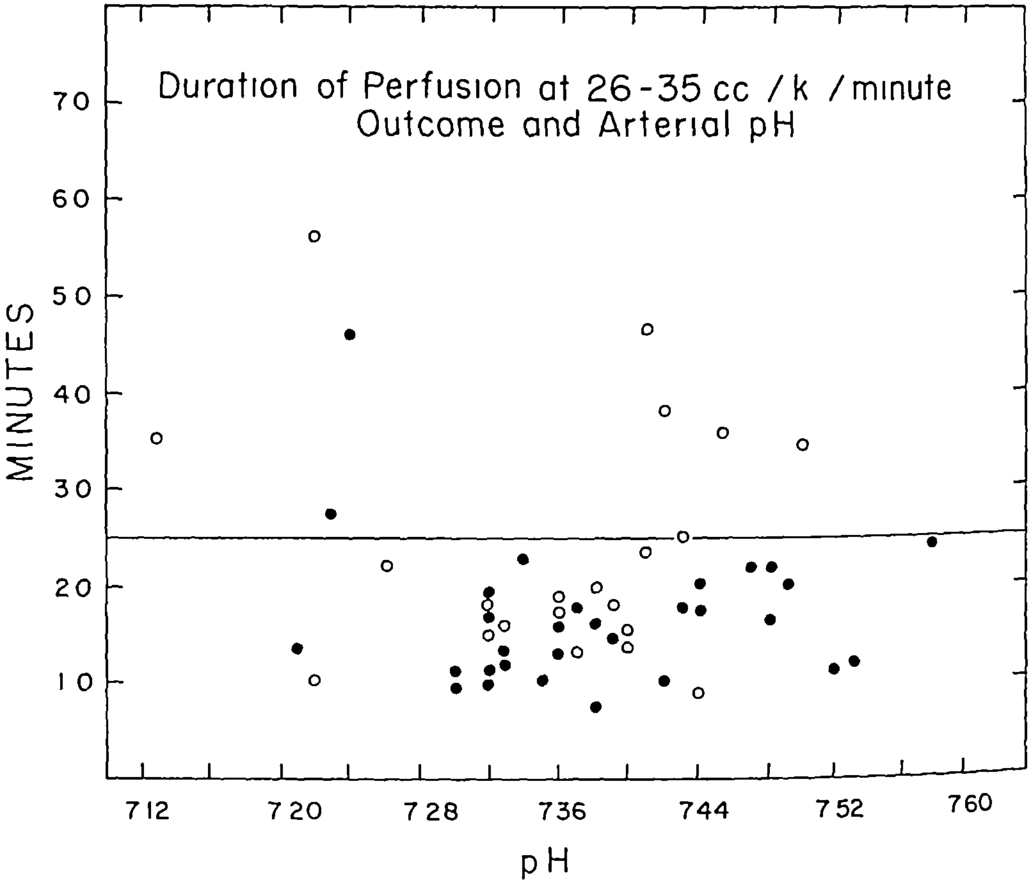


FIG 71 Scattergram relating endarterial pH to duration of flow with identification of all survivals and deaths after a variety of intracardiac procedures (see text) with the use of a DeWall oxygenator

been prepared of the scattergram type using data from perfusions in the respective ranges 26-35 cc /kilo /min , 36-45 cc /kilo /min , 46-55 cc /kilo /min , and 56-65 cc /kilo /min This information was derived from patients operated upon using the bubble-type oxygenator and all data available have been plotted The types of cardiac defects operated upon include atrial septal defect, ventricular septal defect, tetralogy of Fallot defect, ruptured sinus of Valsalva, aortic stenosis (congenital and acquired), mitral stenosis, mitral insufficiency, pulmonary valvular stenosis, infundibular stenosis, total anomalous venous return, atrio-ventricularis communis, and combinations of these lesions The solid dots represent survivors, and the hollow circles connote an individual who ultimately succumbed It is important to indicate that any death occurring during the operation or at any subsequent period (and

that includes individuals dying months following the perfusion) have been listed regardless of the cause In an initial analysis an attempt was made to separate out those deaths which might be specifically identified as of perfusion origin After completing this phase of the study it was apparent that ever more subtle reasons could be derived for either exonerating or including a particular by pass as being lethal in this or that case Furthermore the ques tion of judgment in making these selections is obviously a highly individual one It seemed, on the other hand that if specific trends could be identified despite the burden of placing all deaths regardless of ultimate mechanism against the specific flow rate there could be little residual question about their validity In other words by thus handicapping the various perfusion levels it should be possible to eliminate much of the personal factor which is so

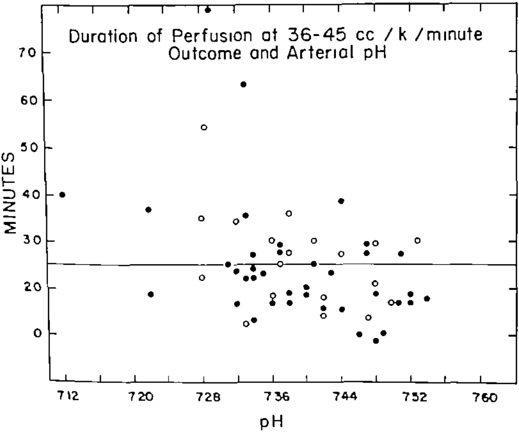


FIG 72 Scattergram relating endarterial pH to duration of flow with identification of all survivals and deaths after a variety of intracardiac procedures (see text) with the use of a DeWall oxygenator

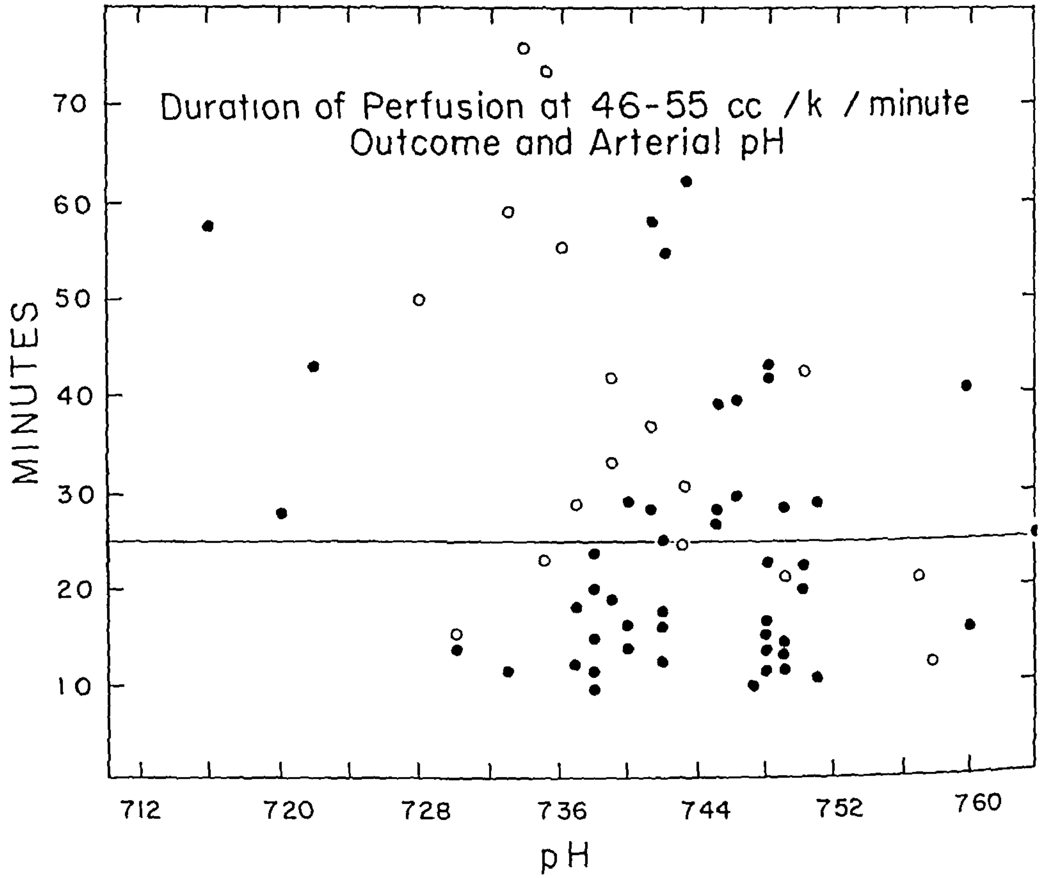


FIG 73A Scattergram relating endarterial pH to duration of flow with identification of all survivals and deaths after a variety of intracardiac procedures (see text) with the use of a DeWall oxygenator

intimately identified with any analysis of results in a series of cardio-pulmonary by-pass procedures This type of analysis appeared to have the additional advantage of presenting each case individually rather than of obscuring its contribution through the use of mean values

Reference to Figure 71 reveals several interesting considerations First, there were but two survivors in nine patients operated upon when the duration of perfusion was twenty-five minutes or longer at this flow of 26-35 cc /kilo /min On the other hand, nine out of ten lived when the duration of the run was under twenty-five minutes and the arterial pH at the conclusion of the perfusion was 7 4 or higher Furthermore, it can be seen that the bulk of the arterial pH values begin around 7 29 to 7 30

When Figure 72 is studied, it is apparent that among those indi-

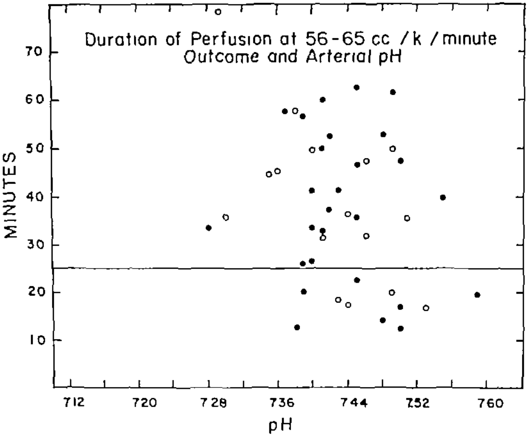


FIG 73B Scattergram relating endarterial pH to duration of flow with identification of all survivals and deaths after a variety of intracardiac procedures (see text) with the use of a DeWall oxygenator

viduals perfused at rates of 36-45 cc /kilo min and for periods of twenty five minutes or over the survivor rate has now been raised to fourteen out of twenty five In addition there is a tendency for the bulk of the arterial pH values to shift somewhat more to the right The data for perfusion rates at 46-55 cc./kilo / min are shown in Figure 73A The survivals now among individ uals perfused for twenty five minutes or longer number twenty out of thirty two This is a higher survivor percentage although there has obviously been a tendency toward a greater number of lengthier perfusions in this series of cases The arterial pH at the conclusion of the perfusion has once again shifted farther to the right with the preponderant majority of values ranging above 7 36 In this regard it is interesting to note also that twenty six living from twenty nine individuals were operated upon at this

flow rate and for periods of twenty-five minutes or less when the pH was 7.36 or higher. In the final chart, quite coincidentally, there are again twenty survivors out of thirty-two patients with an even greater tendency toward the long-term perfusion. It is not parenthetical to add that these protracted runs inevitably represent the more complex type of case and, hence, a priori the risk to the individual should be greater than for the shorter perfusions. Nevertheless, the mortality has remained considerably lower than when the lowest flow was being used. Again, the pH determinations have moved somewhat more to the right.

In summary, therefore, it can be stated that the following plan appears to offer reasonably good protection to the individual undergoing a cardio-pulmonary by-pass using the DeWall bubble-type oxygenator with the Sigmamotor pump. This equipment is calibrated prior to the run to deliver flows at the rate of 50 cc., 60 cc., and 75 cc./kilo/min. For infants and patients with tetralogy of Fallot defects, these perfusion rates are increased to as high as 100 cc./kilo/min. During the course of the perfusion, the response of the individual to that particular rate is monitored both with direct pressure recordings via a polyethylene tube inserted into the arterial system and by means of an electroencephalogram. When either tracing reveals an unsatisfactory appearance, the cause is sought and corrected, i.e., a patent ductus. In the absence of such an obvious leak, the volume flow is raised until an adequate perfusion is achieved. As a consequence of these steps, it is uniformly possible to achieve an arterial pH at the conclusion of the run which will be 7.36 or higher, although the individual may have been on the by-pass for as long as eighty minutes. Furthermore, he can be shown to have maintained a satisfactory electroencephalogram throughout the duration of this period. And, as a somewhat more practical expression of the concept that flows subbasal to the resting cardiac output are well-tolerated, even for prolonged periods of time, is the fact that in the last forty consecutive cases so treated and including a wide variety of cardiac lesions there has been one postoperative death. Therefore, until it is necessary to work within the heart on a procedure requiring well in excess of an hour, this would seem to be an adequate perfusion rate.

It would seem in the present state of our knowledge that there is no more an "optimal perfusion rate" that can be applied to all patients undergoing total cardiopulmonary by pass than there is an optimal dose of penicillin applicable to all patients Such factors as age of patient cardiac reserve type of lesion duration of operation method of collecting blood for replacement type of oxygenator and perhaps other as yet unappreciated factors are important in the determination of an answer to this question Thus at present we prefer to monitor each patient during the particular perfusion utilizing a continuous recording of the electroencephalogram and the systemic blood pressure and adjust thereafter the perfusion rate to keep these variables normal or near normal.

These perfusions too are then further analyzed by study of the metabolic and physiologic data (pH, plasma bicarbonate O_2 controls plasma Hgb platelets etc) obtained before during and after perfusion One should not omit the most important consideration of all namely patient survival. Although this latter depends upon proper surgical technic and postoperative care as well, continuing successes in open heart surgery can rarely be achieved unless the perfusion itself is adequate

This plan outlined has proven satisfactory as judged by a steadily-decreasing risk for open heart procedures

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THE ACID BASE ASPECTS OF EXTRA CORPOREAL CIRCULATION

By

J C. Callaghan, M D., R S Fraser, M.D , J Dvorkin, M D , *and* A G Stewart, Ph D

Changes in acid base balance that are associated with a period of extracorporeal circulation have been observed in both the experimental animal and in human surgical cases Gibbon *et al* [1] in developing a film oxygenator demonstrated a fall in pH to as low as 7.25 during periods of bypass utilizing flow rates averaging 88 cc per kilo per minute Dennis [2] using a different film type oxygenator also noted a fall in pH in dogs to pH 7.2 in the hour following perfusion Those values returned to normal within forty-eight hours They believed that the control of acid base balance rested with the adequacy of pulmonary ventilation prior to perfusion and observed that with adequate ventilation less $NaHCO_3$ was needed during perfusion to maintain a normal pH range DeWall *et al* thought that pH values alone were unreliable for a precise evaluation of acid base balance because of blood buffer compensation They stressed the importance of a fall in base bicarbonate concentration as an index of fixed acid excess A fall in bicarbonate values in the acyanotic cases subjected to total cardio-pulmonary bypass utilizing a bubble-type oxygenator was evident following perfusion In cyanotic patients there was an even more marked decrease in total bicarbonate during perfusion and actually plasma bicarbonate and arterial pH values were lower than normal prior to operation indicating an uncompensated metabolic acidosis Lactate levels in this series were twice normal in the cyanotic group and three times normal in the acyanotic patients following bypass

In a later report these same investigators studied the relationship of perfusion rate to reduction of bicarbonate Their findings

indicated less deficit in bicarbonate following perfusion at rates of 45-50 cc. per kilo. per minute than at the lower flow rates.

Kolff *et al.*,[5] developing a membrane oxygenator, also observed a metabolic acidosis and routinely gave 4.5 mEq. per kilo of sodium bicarbonate during the period of bypass to overcome it. They then repeated this dose three hours post-operatively.

Campbell *et al.*,[6] using a canine lung oxygenator, noted arterial pH values as low as 7.26, and, also, a depression in plasma bicarbonate.

Cross and Kay,[7] in a report of thirty-seven human cases, using a multiple disc oxygenator, observed a fall in pH and blood buffer base. They felt that this metabolic acidosis was due to circulatory stasis and also pointed out that a metabolic acidosis was present in the priming volume of blood standing at normal body temperature in the oxygenator prior to bypass.

Allison *et al.*,[8] in their study of hemorrhagic shock, pointed out that the high lactate levels in hypovolemic animals rapidly fell to normal in the survivors, but never decreased in the dogs that died. Plasma bicarbonate fell and remained low in the dogs that did not survive.

Beatty,[9] in a similar study, observed the rapid return of lactate values to normal in dogs surviving severe hemorrhage.

Seligman *et al.*[10] pointed out the relationship between low blood pressure and lactic acid build-up in dogs subjected to hypovolemia. They stressed that the accumulation of the metabolites such as lactic and pyruvic acids resulted from the combined effects of poor blood flow and an increased rate of production in anoxic tissues. However, DeWall[4] has argued that, if this were true, one would expect a rise in potassium, and stressed that the reverse was true in their cases. Also they observed increasing oxygen consumption up to flow rates of 25 cc. per kilo. per minute but not above this value.

In our series of thirty-five cases of total cardio-pulmonary bypass, an attempt has been made, with the above observations in mind, to study the various components of the acid-base controlling mechanisms. This has been done with a view to determining the inter-relationship between bypass itself, hypovolemic shock and

failing circulation as causative agents in the resulting acidosis both metabolic and respiratory

METHODS

The thirty five cases were operated upon at the University Hospital, Edmonton Canada, for lesions consisting of inter ventricular septal defects interatrial septal defects isolated pul monary stenosis and tetralogy of Fallot. Six were found at opera tion to have lesions not amenable to surgical correction and consisted of tricuspid regurgitation due to atresia complete transposition of great vessels common ventricle with corrected transposition of great vessels Eisenmenger s deformity and mitral regurgitation [11]

The biochemical studies were performed using the methods employed in the ultramicro laboratory of the University of Alberta Hospital Samples were obtained in oiled heparinized syringes and stoppered All analyses were carried out immediately after withdrawal of the sample The pH determinations were done using a glass electrode pH meter Plasma sodium and potas sium were determined using a Baird flame photometer Chlorides were measured by a micromodification of the method of Schales and Schales[12] and carbon dioxide contents were determined with a Kopp-Natelson microgasometer [13]

Early in the study venous samples were used but subsequently arterial samples were obtained An indwelling arterial catheter utilized for pressure recordings from the right brachial artery during the surgical procedure was left in place and provided a satisfactory method of repeated arterial sampling in the early post-operative period

The bubble oxygenator exactly as developed and used at the University of Minnesota Hospital Minneapolis was used for the cardio-pulmonary bypass in this series Arterial inflow was by means of the common femoral artery Acetylcholine[14] was used for elective cardiac arrest where indicated.

Blood volume studies were by radioactive chromium supervised by Dr Edward Bell Director of Laboratories University of Alberta Hospital

RESULTS

Changes in Sodium

There was little if any change in serum sodium, following total cardio-pulmonary bypass in any of the cases studied The mean values preoperatively of 145 mEq per liter were changed very slightly in the first post-operative sample taken in the first few hours following perfusion. Twenty-four hours following perfusion there was a very slight drop in the mean sodium values to 142 mEq per liter. This is illustrated in Figure 74 which represents the mean values of twenty-eight cases

Changes in Potassium

The mean preoperative value for the cases studied was 4 7 mEq per litre In the first post-operative sample at three hours following perfusion the mean value was 3 9 mEq per liter Values had returned to pre-perfusion values by twenty-four hours later This is shown in Figure 74 In three cases the potassium fell to 2 4,

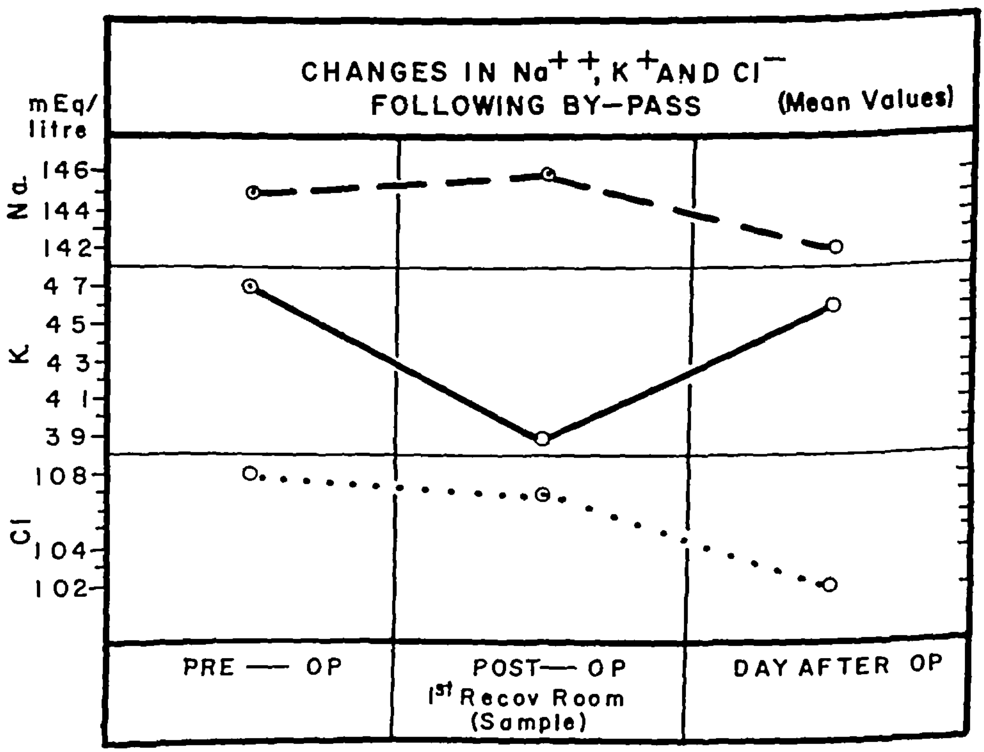


Fig 74 See text

2 6 and 2.9 and these patients were given a potassium containing fluid in the post-operative period In two other instances potassium rose without explanation to abnormally high levels of 6 3 and 6 7 mEq per liter

Changes in Chloride

The mean values of chloride dropped slightly from a mean value of 108 mEq per liter preoperatively to 107 mEq per liter three hours after perfusion and to 102 mEq per liter twenty four hours later This is shown in Figure 74

Changes in pH

During the period of bypass the oxygenator appeared to function as an excellent means of removing CO_2 and through this medium the pH remained for the most part fairly constant during bypasses of thirty minutes or less A respiratory alkalosis was created by the anesthetist prior to bypass Figure 75 shows a representative change in arterial pH during and after bypass In

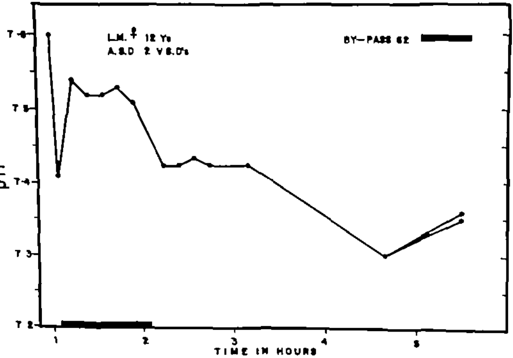


FIG 75 Arterial pH changes during total bypass

bypasses lasting longer than thirty minutes there tended to be a fall in arterial pH of a slight degree

A fall in arterial pH within three hours after perfusion occurred in five of twelve cases studied at the time of their return to the cardiac recovery room In three of these five cases the fall in pH was associated with an elevation in pCO_2 indicating a superim-

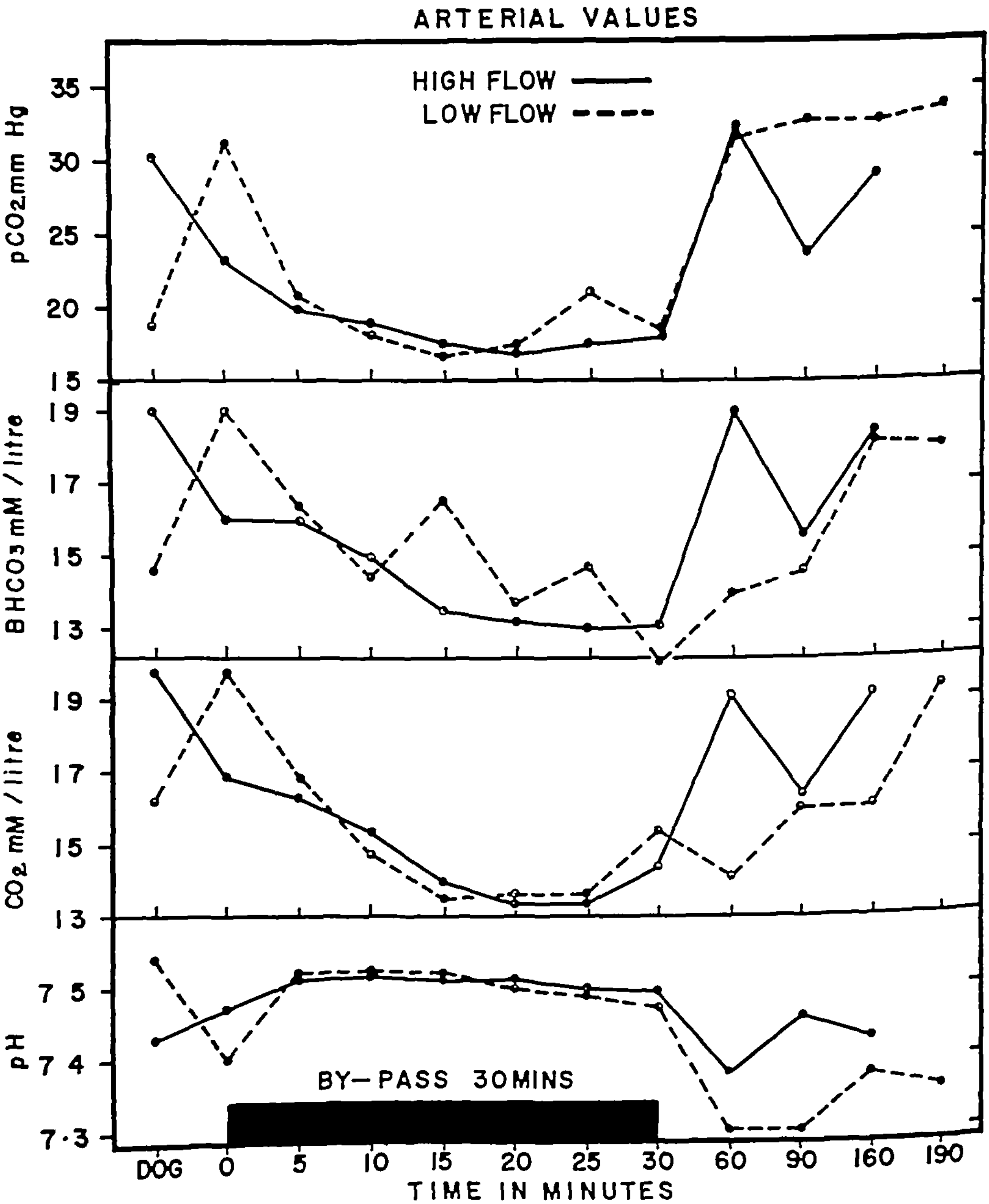


Fig 76 Acid-base changes in eight dogs at different perfusion rates

posed respiratory acidosis All three of these children died in spite of the addition of sodium lactate or sodium bicarbonate solutions All three were "not cured" by the operative procedure

In order to study more closely the changes in pH and CO_2 content during the period of bypass similar procedures were performed in eight dogs by Elliot[15] in our laboratory He was able to demonstrate the efficiency of the oxygenator in eliminating CO_2 and maintaining a constant pH during the thirty minute total body perfusion The same fall in pH and rise in CO_2 tension that we observed immediately after perfusion in human cases also appeared in this animal series This is shown in Figure 76 where high flow is 70 cc per kilo body weight per minute and low flow 35 cc. per kilo body weight per minute

Either sodium lactate (1 Molar Solution) or sodium bicarbonate (44.6 mEq per 50 cc) were given to twenty two of thirty cases The changes in arterial pH resulting from the addition of base are shown in Figure 77

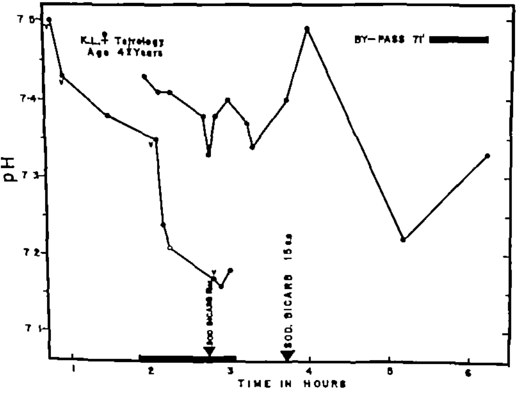


FIG 77 Changes in arterial and venous pH during total cardio-pulmonary by pass.

It was possible to alter the arterial pH by the addition of base, and a review of the number of survivors in the group receiving base compared to the number that survived without this treatment is shown in Figure 78 The series is too small to offer any concrete conclusions concerning the therapeutic value of this treatment

CASES GIVEN BASIC IONS		
	Cases	Survivals
Na Lactate	12	7
$NaHCo_3$	8	5
Both	2	2
Neither	8	4
	30	18

FIGURE 78

Changes in Base Bicarbonate

Of the twelve cases studied on return to the cardiac recovery room, one to three hours following perfusion, six had base bicarbonate values of less than 20 mEq However, only two of these six had an arterial pH value below normal, indicating an uncompensated metabolic acidosis The remaining four had low pCO_2 levels compatible with respiratory compensation for the increase in fixed acids which had depleted their base bicarbonate These changes are demonstrated in Figure 79

Similar changes of base bicarbonate were demonstrated in each of the eight animals subjected to total cardiopulmonary bypass The decrease in bicarbonate during bypass was followed by a return to pre-perfusion values within sixty minutes from the termination of perfusion The rise was more rapid in the group perfused at the higher flow than in the four animals perfused at the low flow rate (35 cc per kilo body weight per minute)

CHANGES IN ACID BASE BALANCE

Values on 12 Cases on Return to Cardiac Recovery Room

Arterial pH	mEq/L CO_2	mEq/L $NaHCO_3$	mmHg pCO_2	
7.21	24 4	22.5	60	×
7.32	20 0	18 8	40	
7 47	19 8	19 2	27	×
7 41	17 3	16 7	29	
7 51	22 5	21 7	29	
7.29	32 7	30.5	68	×
7 40	24 5	22 8	40	
7 42	15.5	15 0	27	×
7 43	14 0	13 4	22	
7 32	27.5	26 0	53	
7 46	22 3	21 4	32	
7.22	18 8	17 5	46	×

FIGURE 79

COMMENT AND SUPPORTING DATA

In order to compensate for acid metabolites the body maintains a relatively constant pH by a system of buffers During total cardio-pulmonary bypass the pH is maintained within relatively normal limits by the adequacy of the oxygenator in eliminating CO_2 There appears to be a decrease in this function during prolonged perfusions Base bicarbonate appears to fall in a fairly regular fashion during bypass as shown in Figure 76 One must assume that fixed acid excess is the cause for this base bicarbonate deficit

However the patient who comes off bypass "cured" appears to have the ability to handle the fixed acid production with ease This is reflected in the fact that sixteen of our seventeen single lesions who were cured by the procedure survived. The fact that only two of these sixteen patients developed any significant degree of acidosis would seem to reflect the stability of their circulation following bypass

In those patients who developed progressive circulatory collapse with decreasing pH values the use of lactate or bicarbonate

did not appear to influence the course The acidosis appeared to represent merely a sign of the deteriorating circulatory state

It is difficult to say how comparable the state of total cardiopulmonary bypass is to experimental hypovolemic shock In all our cases the usual measurements of blood loss were made in an attempt to maintain normal blood volume In fifteen cases measurement of circulating blood volume was made before and after

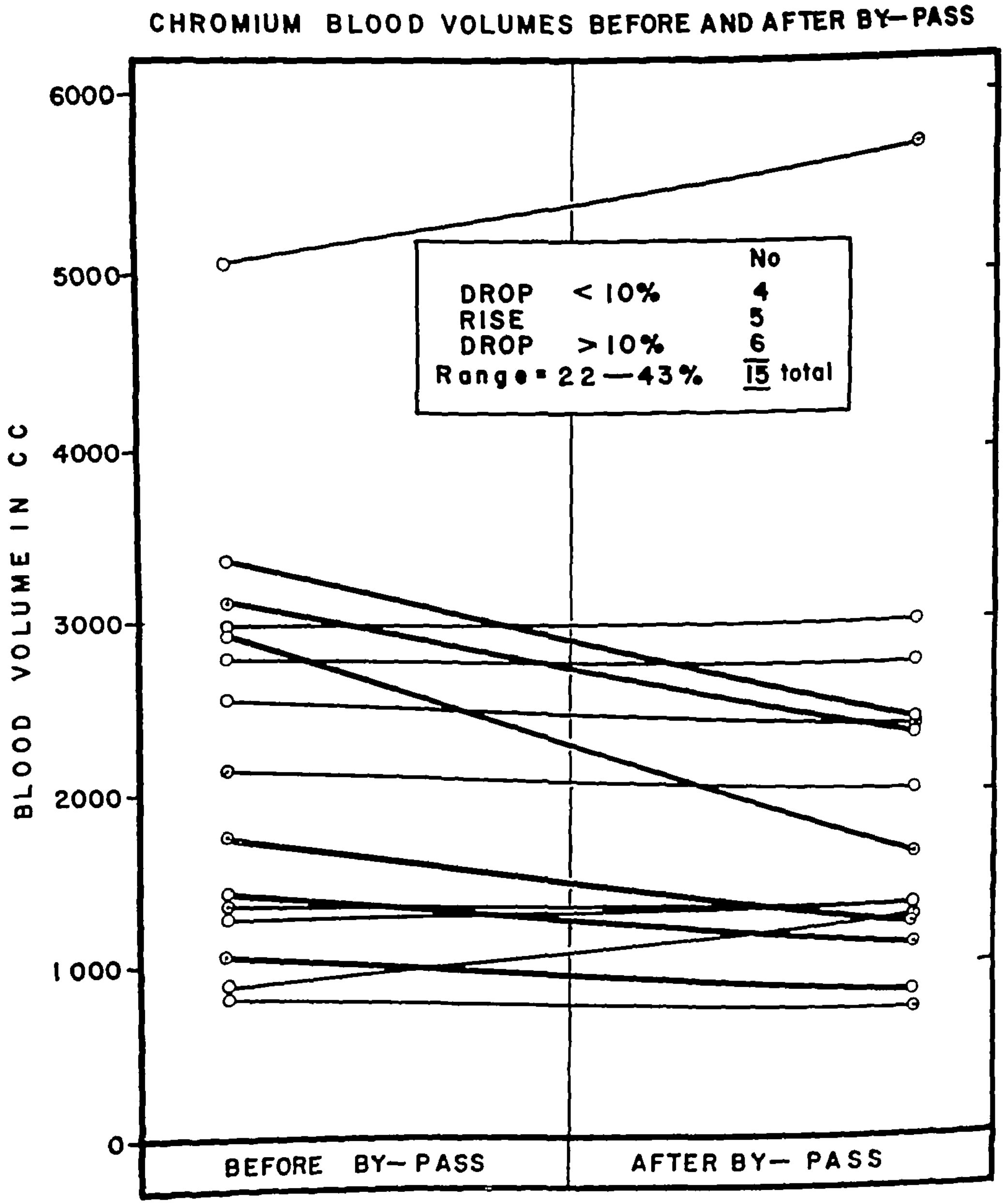


FIGURE 80

bypass by use of radioactive chromium technique In six cases the post perfusion circulating volume had decreased to less than 90% of the preoperative volume These findings are shown in Figure 80

During bypass total flow is less than resting cardiac output and peripheral resistance is increased The condition resembles hemor rhagic shock with accumulation of acid metabolites with a de crease of base bicarbonate The fall in potassium is the only feature that is difficult to explain

The problem of metabolic acidosis due to anaerobic glycolysis in the donor blood during the period elapsing between withdrawal from the donor and actual insertion into the patient has been con

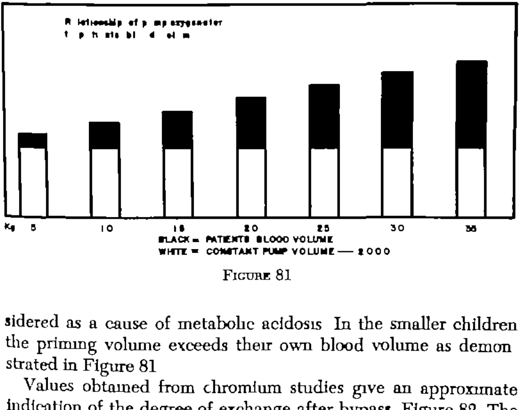


Figure 81

sidered as a cause of metabolic acidosis In the smaller children the priming volume exceeds their own blood volume as demon strated in Figure 81

Values obtained from chromium studies give an approximate indication of the degree of exchange after bypass Figure 82 The fact that only 12-35% of the patient s original blood remains fol lowing bypass suggests the importance of assessing the anion cation content of the donor blood

Measurements of pH were made on blood drawn in the same manner as that used for bypass The initial mean pH of eleven samples fell from 7 53 to 7 42 at the end of four hours as shown in



FIGURE 82

Figure 83 However small this pH fall may be, the underlying accumulation of lactate due to anaerobic glycolysis is of the order of 16 5 mgms per 100 cc of blood per hour of incubation at 37 5° C [16]

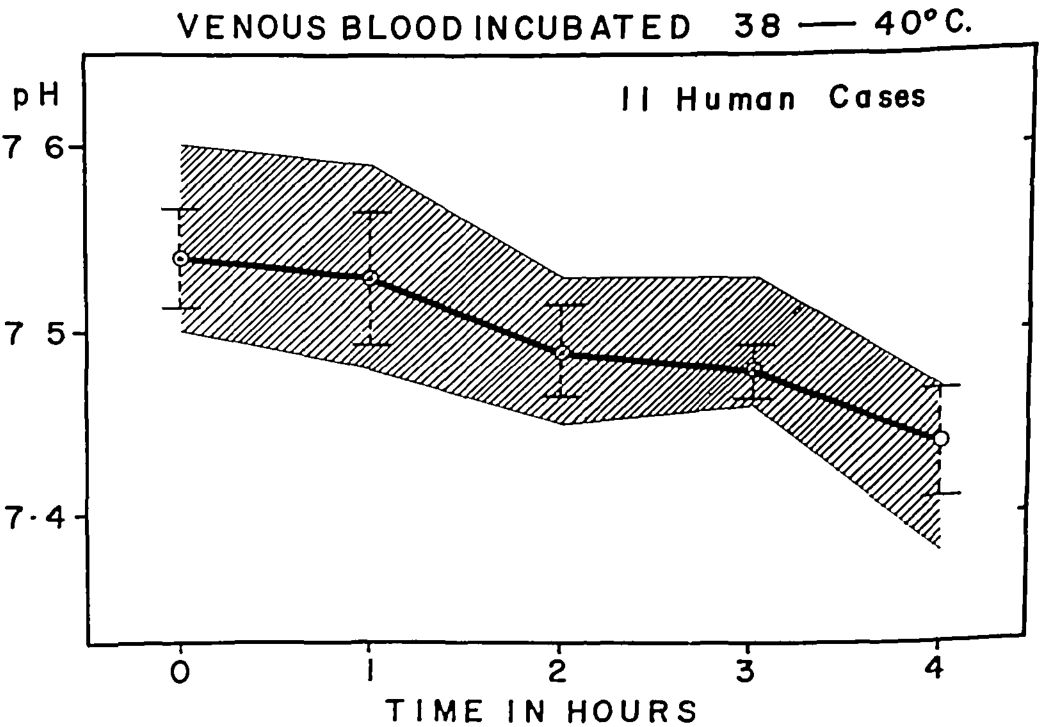


FIGURE 83

It is suggested that the lactate from the donor blood in addition to the acid metabolites accumulated during low tissue perfusion may contribute to the increase in anion content of the circuit This is now the subject of a separate investigation

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HYPOTHERMIA IN RELATION TO LOW FLOW RATES

By

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INTRODUCTION

THAT hypothermia of the patient might in many ways facilitate mechanical by pass of the heart and lungs with a pump oxygenator has long been recognized. However most surgeons have agreed with Bigelow's statement that from the standpoint of clinical application it would appear at present, to be combining the risks of two dangerous procedures.[1] Whole or partial perfusion of the hypothermic patient or experimental animal with small amounts of oxygenated blood during the time of venous inflow occlusion has resulted in improved results over those of hypothermia alone.[2,3,4,5] Sealy and associates[6] and Sakakibara[7] have used the combination of hypothermia and mechanical by pass of the heart and lungs with a pump oxygenator clinically with good results. Gollan and associates[8,9] have reported experimental studies with the pump oxygenator and hypothermia. The present report is concerned with the experimental evaluation of the combination of these two techniques.

METHODS

Mongrel dogs were used. They were anesthetized by the intravenous administration of thiopental sodium. Tracheal intubation

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was carried out and the lungs were rhythmically inflated with oxygen, or oxygen and ether as necessary, by means of a mechanical insufflation apparatus. Those animals which were cooled were placed in a tub of crushed ice and water. The esophageal temperature was allowed to drop to 33.5° or 33° C. The dog was then removed from the cooling solution and was placed on the operating table. The temperature continued to drop and usually stabilized between 28° and 30° C. Thoracotomy was carried out through the fourth or fifth intercostal space. Aseptic technique was not used. Many animals developed obvious infections in the postoperative period and the survival data were undoubtedly modified by this. Femoral arteries were isolated and cannulated as needed for use with the pump oxygenator or for use in measuring arterial blood pressure. Operations were performed with careful attention to hemostasis. The pericardium was opened with the cutting current and bleeding vessels were carefully coagulated. Before insertion of arterial or cardiac catheters, the dog was heparinized with a dose of 1.5 mg./kg. Plastic catheters were introduced into the vena cavae, that in the inferior through the auricular appendage and that in the superior through the right atrial wall. At the time of chest closure, a large tube was placed in the thoracic cavity for use in aspirating blood or air. Protamine sulfate was administered in milligrams equal to the milligrams of heparin given. If the dog was hypothermic, it was warmed by immersion in hot water. Procaine penicillin, 300,000 units, was administered to the animal following the operation. No further antibiotics were given.

Sigmamotor pumps were used. The oxygenator was of the large bubble type. It was modified from that of DeWall and associates[10] (Fig. 84). The major differences were that the oxygen was filtered into the blood stream through larger holes, a stainless steel sponge coated with Antifoam A was placed in the large debubbling tube, and the blood reservoir was usually a vertical one. In a few procedures, the reservoir was of Mayon tubing, one inch in diameter, wound into a helix as in DeWall's Type 3 oxygenator.[10] The blood filter was furnished by the Abbott Company for pump oxygenator use and was made of stainless steel screen. It was placed between the reservoir and the arterial pump. The

oxygenator was fashioned from variously cut lengths of Mayon tubing This was cleaned with a detergent solution after use however it was not sterilized by autoclaving or by germicidal solutions In a number of the animals the blood from both vena cavae drained by gravity into a small reservoir placed about 40 cm below the level of the operating table The gravity flow unit

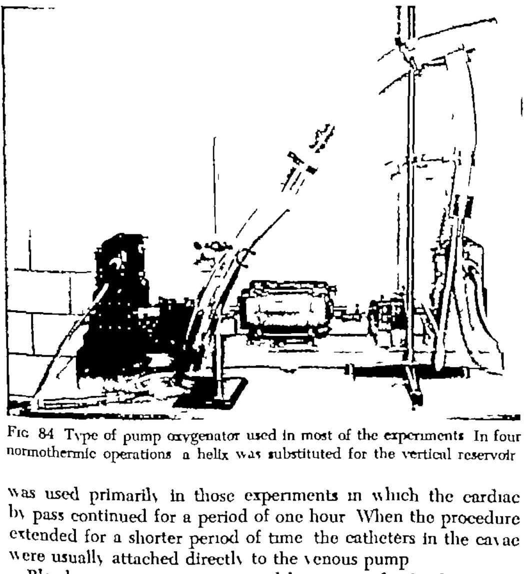


FIG 84 Type of pump oxygenator used in most of the experiments In four normothermic operations a helix was substituted for the vertical reservoir

was used primarily in those experiments in which the cardiac by pass continued for a period of one hour When the procedure extended for a shorter period of time the catheters in the cavae were usually attached directly to the venous pump

Blood pressures were monitored by means of a Statham pressure transducer recording on a Sanborn Twin Viso Cardiette The oxygen saturation of the arterial and of the mixed venous blood was measured in some animals The Roughton Scholander method was used

A part of this study was devoted to evaluating three cardioplegic drugs. Cardiac by-pass was begun at a blood flow rate of 30 cc./kg./min. One of the drugs was injected into the ascending aorta after the aorta had been clamped just distal to the point of injection. Fifteen minutes later, the aortic clamp was removed. As soon as a satisfactory normal heartbeat was restored, the pump perfusion was discontinued. Potassium citrate was used in the concentration recommended by Melrose.[11] Two cc. of a 25 per cent solution was mixed with 18 cc. of blood. A similar concentration of potassium lactate was used. This drug was obtained in a concentration of 2 mEq. per cc. Five mEq. were mixed with blood to make 20 cc. Twenty per cent calcium gluconate solution was frequently added to the oxygenator reservoir near the end of the fifteen minute period. Acetylcholine in a concentration of 100 mg. per cc. was mixed with 19 cc. of blood and the resulting solution was injected into the aorta. In most dogs, a total of 100 mg. of acetylcholine was administered. In a few large animals, 10 mg. per kg. was administered. In all, 0.4 mg. of atropine sulfate was added to the blood in the oxygenator reservoir one minute before the release of the aortic clamp. During the time of cardiac arrest, the blood in the right heart was allowed to drain into the thoracic cavity through a small right atriotomy incision. Immediately after the clamp was released from the aorta and coronary flow was once again established, the occluding tapes about the superior and inferior vena cava were released to prevent cardiac dilatation.

EXPERIMENTAL OBSERVATION

Survival data are compiled in Table 1. In a control group of eleven animals, the body temperature was maintained near normal and the heart was by-passed for one hour. In five, perfusion was carried out at a rate of 40 cc. per kg. per min. Three died within a few hours. One lived about twenty-four hours, and one survived for four days. The latter two animals demonstrated generalized muscle spasticity. Six dogs were perfused at the faster rate of 70 cc. per kg. per min. Four died within a few hours. One lived for twenty-four hours, and one for three days. The latter was spastic during the time of survival. Many of the animals died in a shock-like state. Examination of the thoracic cavity often failed to

explain the cause of death Partial consolidation of the lungs was frequently present None of the spastic animals was able to sit, walk, or feed itself Of the total number of eleven animals which were by passed at normal body temperature seven died within a few hours after operation two within one day and only two survived three or more days Three of those animals which survived for twenty four hours or more were spastic and one

TABLE 1

SURVIVAL STUDY

Temperature	*Number of Dogs*	*Pump Flow cc/kg/min*	*Deaths*		*Survival 3 or more days*
			Few Hours	*24 hrs*	
		Cardiac By-Pass for One Hour			
Normothermia	5	40	3	1	1*
Normothermia	6	70	4	1	1
Hypothermia	5	15	0	1	4
Hypothermia	12	30	0	0	12
Hypothermia	11	40	4	3	4
		Cardiac By-Pass for 30–30 Minutes Right Ventriculotomy for 20 Minutes			
Hypothermia	10	30	1†	0	0

* Spastic.
† Pneumothorax.

never completely awakened A helix reservoir was used in four of these operations Three died in a few hours and one lived for three days

In eighteen animals the body temperature was lowered to an average of 29 C Mechanical by pass of the heart and lungs with the pump oxygenator was then carried out for one hour In five a pump flow of 15 c c per kg per min. was maintained One died at twenty four hours and four lived for three or more days Of the four survivors only one was entirely normal and vigorous during the postoperative period Three were weak and did not walk spontaneously Twelve dogs were perfused at a rate of 30 c c per kg per min All were long term survivors Most of these animals were normal and active shortly after operation Eleven dogs were by passed at a rate of 40 c c per kg per min Four died within a few hours after operation Three lived for twenty four hours and four for a number of days Autopsies of the seven

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ing this time In those with a blood flow of 40 cc per kg per min the average mean pressure during the time of cardiac pulmonary by pass was only 49 per cent of that before this time The fall in blood pressure was not so great when the rate of pump flow was 70 cc per kg per min In this group it was sixty six per cent of that before the time of cardio pulmonary by pass Twenty five hypothermic animals were similarly studied. A flow rate of 15 cc per kg per min resulted in a sixty five per cent decrease in pressure At 30 cc per kg per min the average mean pressure during perfusion was eighty seven per cent of that before and in those by passed at a flow rate of 40 cc per kg per min the pressure during the time of perfusion was actually greater than that before

TABLE 3
AVERAGE BLOOD OXYGEN SATURATIONS AT DIFFERENT TEMPERATURES AND PERFUSION RATES

Temperature	*Number of Determinations*	*Perfusion Rate cc /kg /min*	*Blood Oxygen Saturation in Percentage Saturation*		
			Artery	*Vein*	*Difference*
Normothermia	0	40	86	28	58
Hypothermia	0	15	102	40	62
Hypothermia	27	30	90	57	33
Hypothermia	5	40	96	64	32

cardio-pulmonary by pass being one hundred and twenty four per cent of normal

Oxygen saturation of arterial and mixed venous blood was determined forty four times during the time of cardio-pulmonary by pass (Table 3) Arterial blood oxygen saturation was near one hundred per cent in most instances In some oxygenation of the blood was not satisfactory and these few determinations lowered the average Unsatisfactory oxygenation resulted from an inadequate flow of oxygen into the apparatus a technical error In normothermic dogs which were perfused at 40 cc per kg per min the average arterial oxygen saturation was eighty six and the mixed venous saturation was twenty-eight per cent In hypothermic animals which were by passed at a rate of flow of 15 cc per kg per min the arterial oxygen saturation was one hundred

which died within twenty-four hours did not satisfactorily explain the cause of death

Ten hypothermic animals had cardio-pulmonary by-pass carried out for a period of approximately thirty minutes Six were perfused for exactly thirty and four for thirty-three to thirty-nine minutes A large right ventriculotomy incision was made in all and the heart was kept open for twenty minutes During the time the heart was open, blood was aspirated from the heart and returned to the pump oxygenator apparatus In four experiments, the rate of this flow was measured, and was found to vary from 6 4 per cent to 11 per cent of the pump flow Ventricular fibrillation occurred in one animal as the venous catheters were being

TABLE 2

AVERAGE MEAN BLOOD PRESSURES AT DIFFERENT TEMPERATURES AND PERFUSION RATES

Temperature	*Number of of Dogs*	*Rate of Pump Flow (cc /kg /min)*	*Average Mean Blood Pressures*		*Per Cent of Pre-By-Pass Pressure*
			Before By-Pass (mm /Hg)	*During By-Pass (mm /Hg)*	
Normothermia	4	40	120	59	49
Normothermia	5	70	121	80	66
Hypothermia	6	15	94	62	65
Hypothermia	12	30	112	97	87
Hypothermia	7	40	101	125	124

inserted One shock of two hundred volts restored this heart to a normal rhythm The experiment was satisfactorily completed and the animal survived for a period of fifteen days Ventricular fibrillation did not otherwise occur Following operation, one died in the immediate postoperative period from a bilateral pneumothorax The other nine lived for three days or longer and most survived until the time of sacrifice, a period of fifteen days

Arterial blood pressure was monitored in most of the animals Mean pressures were averaged and the results are shown in Table 2 The average mean pressures of the hypothermic animals was about 19 mm of mercury below those of the normothermic controls Most of the dogs which were by-passed at normal body temperature underwent a substantial fall in blood pressure dur-

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occurred on the operating table. Three dogs which did not develop ventricular fibrillation had a rapid return of normal heart beat following release of the aortic clamp. This occurred in forty-five seconds with one, in twenty seconds with another, and in three minutes with the third. Those which fibrillated required a much greater length of time to restore normal rhythm and the average for the group was 9.5 minutes. Xylocaine blockade of the sino-auricular node was carried out in four of these and ventricular fibrillation occurred in three. Acetylcholine was used to induce cardiac arrest in eleven animals. Complete arrest occurred immediately following injection. In most cases a slow return of cardiac activity began about five minutes afterwards. By the end of the fifteen minute period a rate of two to ten beats per minute was usually present. In two instances it was necessary to give more acetylcholine. Ventricular fibrillation occurred once for a frequency of nine per cent. Complete recovery of the heart was rapid and a normal beat was restored on an average of 1.2 minutes following release of the aortic clamp.

DISCUSSION

Control observations indicated that cardio-pulmonary by-pass of one hour in normothermic dogs was followed by a high rate of morbidity and mortality. Undoubtedly more animals would have survived if certain methods had been instituted, such as aseptic operating room technique, sterilization of the pump-oxygenator tubing, more care in the postoperative period, etc. Substitution of a helix for the vertical reservoir in a few cases did not improve the overall poor results. Other studies with normothermic animals and with similar pump oxygenator equipment have also shown a high rate of morbidity and mortality with cardio-pulmonary by-pass of only twenty minutes.[4,1] A striking improvement in survival was obtained when cardio-pulmonary by-pass was done in hypothermic dogs. This marked improvement in results was especially evident when a flow rate of 30 cc. per kg. per min. was used. At this rate hypothermic dogs withstood right ventriculotomy with a low incidence of ventricular fibrillation and with an excellent rate of survival. The cause of the increased mortality in those perfused at 40 cc. per kg. per min. was not clear. The

and two and the mixed venous oxygen saturation was forty per cent In those perfused at a rate of 30 cc per kg per min, the arterial oxygen saturation was ninety and that of the mixed venous blood fifty-seven per cent In those with a flow rate of 40 cc per kg per min, the arterial oxygen saturation averaged ninety-six and that of the mixed venous blood sixty-four per cent

Cardiac arrest was induced in thirty-four hypothermic animals during the time of cardio-pulmonary by-pass (Table 4) In all, the rate of flow of the pump was 30 cc per kg per min The heart was excluded from the general circulation for fifteen minutes The

TABLE 4

INDUCED CARDIAC ARREST IN HYPOTHERMIC ANIMALS
PUMP FLOW 30 CC /KG /MIN
AORTIC OCCLUSION 15 MINUTES

Number of Dogs	*Drug*	*Perfusion Time in Minutes*	*Average Heart Recovery Time in Minutes*	*Percentage of Fibrillation*
13	Potassium citrate	27	8 7	23
10	Potassium lactate	35	9 5	70
11	Acetylcholine	22	1 2	9

body temperature ranged between 28° and 30° C Potassium citrate solution was used to stop the heart in thirteen dogs An average of 18 7 cc of the blood potassium citrate mixture was used The average time for the heart to recover a normal rhythm and vigorous beat was 8 7 minutes Ventricular fibrillation occurred in three animals following release of the aortic clamp As this portion of the study progressed, it was our impression that the addition of 5 to 10 cc of twenty per cent calcium gluconate to the arterial reservoir about one minute before the time of removal of the aortic clamp resulted in a quicker return of normal cardiac contractions In ten hypothermic animals, a mixture of potassium lactate with blood was used At the end of the fifteen minute period, twenty per cent calcium gluconate was often given It was injected directly into the proximal aorta in some and in others, was added to the blood reservoir Ventricular fibrillation occurred in seven following release of the aortic occlusion In all but one, it was possible to shock the heart and restore normal rhythm Cardiac rhythm of one animal did not convert to normal and death

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14 Riberi, A and Shumacker H B Jr Elective cardiac arrest under moderate hypothermia. Submitted for publication

elevated blood pressure that most of these dogs maintained during cardiac by-pass suggested that the pump flow was excessive

Arterial blood pressure was well maintained in hypothermic animals during the periods of by-pass At a flow rate of 30 cc per kg per min, it did not vary greatly from pre-perfusion levels

Preliminary observations of induced cardiac arrest in hypothermic dogs indicated that a high rate of ventricular fibrillation followed the administration of the two potassium-containing drugs Recovery of strong normal contractions was often slow The high rate of ventricular fibrillation associated with potassium lactate was in contrast to the good results previously obtained in this laboratory[14] This may be explained by the shorter period of cardiac arrest in the earlier investigation Acetylcholine arrest was followed by a short recovery time, but the arrest was rarely complete. None of the three drugs as used in these experiments was entirely satisfactory Further study is needed of their use in the hypothermic state

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DISCUSSIONS ON PHYSIOLOGY OF PERFUSION

DR JULIO C DAVILA, Philadelphia Dr Swan and gentlemen First, I would like to thank the Committee on Arrangements for the privilege of being here

It has been most impressive to note the amount of work that has been going on through the country and in the many foreign countries represented here Particularly impressive have been the clinical results which are being obtained in several centers, but also impressive is the variety of work that is being done, in the sense not only of its nature but of the methods being compared, or at least attempted to be compared This, I believe, is one of the major handicaps, that is, the inability to compare experimental and clinical results We are attempting to learn more about this field, and are somewhat handicapped because it is difficult to choose, to compare and to evaluate what data are available

For the last two and one-half years here we have limited our work on extracorporeal circulation to the experimental laboratory We have chosen, arbitrarily, the easiest, the most disposable and inexpensive method to use, the DeWall oxygenator and the Lillehei single pump Our experience in many animals has been most interesting We have attempted to control our experiments and to study metabolic changes in much the same way as has been shown by many workers who have preceded us

The following are some of our observations and some of the tentative conclusions which we entertain at this time We have observed the most common cause of death in our dogs to be shock, whatever that means Atelectasis is second, and brain damage is very important even though it is in third place We have found pulmonary edema to be much less important We have done extensive measurements with these parameters, and, as many of you have found, there is a tendency during the preperfusion period toward the development of a metabolic acidosis which remains compensated until the end of the perfusion Afterwards, in our experience there is a marked decompensated metabolic acidosis We have also observed a very pronounced increase in the A-V differences, and it is rather difficult to control circulatory pressures A rather marked fall in body temperature occurs after a period of time following perfusion, usually within an hour, although the metabolic acidosis may be improved However, the other changes are not improved

I had many other conclusions but I believe that the problems we should attack first are related to redesign of important equipment improvement of certain technics and probably certain improvement in operative procedures and methods

DR HANS C ENGELL, Copenhagen Denmark Dr Swan, and gentlemen! I went home last night and tore up my paper because the Minneapolis group spoiled the game

An ideal physiological experiment requires that all variable factors, be kept constant except the one to be investigated

In the perfusion of intact animals or humans so many variable factors are included that it can never be a physiological experiment in the classical sense Still we have to make a physiological approach to the problems and try to keep a uniform standard of technic for our procedures I am sure most of us think we are doing so but very few of us are, in fact. The weak point is the complexity of teamwork. Only a well-drilled, highly disciplined team can keep the standards If we get a new anesthetist or surgeon, or technician we have in reality altered the technic. When we have failures then we are apt to look for some new and not thought-of complication Was it due to denaturation of protein or to pyrogens or maybe to oxygen intoxication? Well I do not say there are no such problems but it is amazing to see that Dr Lillehei's group are able to perfuse forty patients with only one death. They have a fairly good oxygenator a rather poor pump and too small flow rates Still their results are excellent. This proves the all importance of teamwork and technical skill, and it makes it a bit difficult to discuss in earnest the refined details in physiology of perfusion before we are all as clever as the Minneapolis group

Another item of importance The basal metabolic requirements should be covered during perfusion From experiments on dogs it is known that basal metabolic rate does not change very much during anesthesia.

When Dr Kirklin's group published the results of their first 40 human perfusions it was striking that the oxygen consumption calculated from their results corresponded so closely to the calculated oxygen consumption during basal condition

We do not yet have extensive experience with human perfusion, but it is my experience both from Dr Gibbon's laboratory and from Copenhagen that the dogs surviving total perfusion are those with high flow rates and oxygen consumption of at least 5 cc/kg/min When

some people experimentally have found higher survival rates with low flows, it may be because of complications with air embolism at high flow, as pointed out previously by the Los Angeles group

The problem of acidosis goes with the perfusion rate Metabolic acidosis beyond the slight changes always seen during anesthesia is usually due to inadequate minute volume To find in which stage hypoxia comes in, one has to be careful in timing of the blood sampling The caval flows are considerably obstructed by the venous catheter before the extracorporeal circulation is established If one of the blood samples is taken before the venous catheters are placed in the cavae, the next during perfusion, an acidosis due to inadequate circulation prior to the perfusion may not be revealed as such

At last, why talk about the azygos flow principle? One might as well talk about the principle of starvation It is possible to survive starvation, but it is too much to make a principle of it

DR ROBERT S LITWAK, Miami Dr Swan, and gentlemen I should certainly like to acknowledge the debt that our young group owes to this august body for the privilege of attending this meeting and for that of the floor I should also take this opportunity to acknowledge our specific debt to the University of Minnesota group for their very, very great help in getting us started with their unit

We are using unmodified the Minnesota apparatus We have found that during a reasonably long perfusion of one hour, the flow is in excess of 70 ml /kg /min We had no reason to explain this We found very minute bubbles in the vertical portion of the helix just proximal to the arterial pump I felt certain that other investigators had not bumped into this problem, but we could not explain why these bubbles appeared This finding could be correlated to the EEG data, that is to say, at least inferentially, and it suggested possibly we were having trouble with the minute bubbles because of some technical error We obviously questioned our own technical capacity in handling the unit Nevertheless, when the University of Pennsylvania group suggested the possibility that one perhaps could prevent the minute air emboli by interposing a reservoir beyond the helix, we went back to one of the older DeWall models and arranged a vertical reservoir, and in this series it is interesting to see the improvement that we have been able to obtain We are now using this reservoir In a small series of animals the survival rate obtained is approximately 75 per cent in dogs undergoing perfusions for periods between 45 minutes and one hour This 75% rate excludes the technical failures which have occurred

The only thing I should like to point out here is simply the variation that we have gone back to the simple vertical reservoir Figure 85 We dont change the circuit a great deal but here at the helix we inject the blood fairly high in the reservoir We do not use a filter in

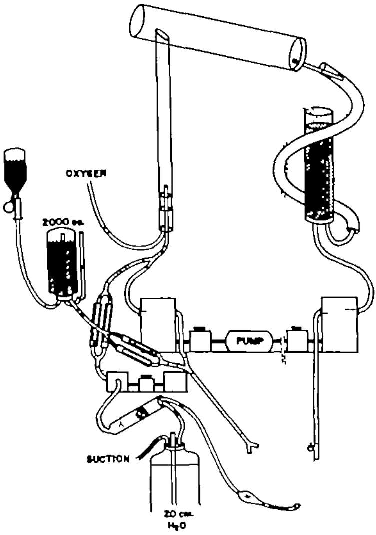


FIGURE 85 (DR LITWAK)

the arterial circuit However when the blood flow is from our reservoir into the venous side we filter it In a cardiotomy the blood is filtered before it is put back in the oxygenating unit.

I will not bore you with the metabolic data but simply there may have been changes here in like manner to those described previously this morning In our dogs whose blood pH s dropped after a run, they

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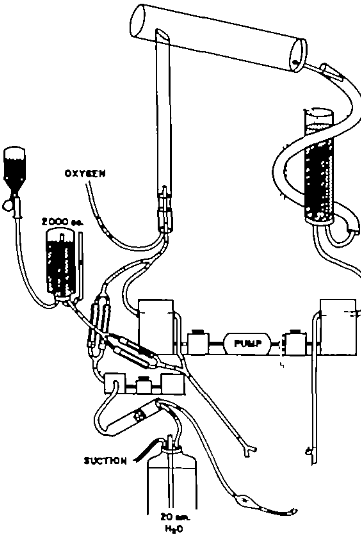


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almost invariably died These deaths could be ascribed to the pulmonary parenchymal changes, to what seemingly was a respiratory death Therefore, it is not surprising that the administration of sodium bicarbonate in an attempt to surmount this acidosis did not alter the survival rate

Perhaps one philosophical thought might be mentioned in this physiological discussion, and it is this I think the scatter diagrams shown by Dr Varco might also be meaningful in an attempt to achieve more suitable data in the evaluation of the final flow rates We found certainly that our mean aortic pressures have varied considerably, and I think it could be that the EEG changes can be correlated When one talks in terms of flow rates alone, perhaps we should speak in terms of parameters and pO_2's in the particular patient being discussed Thank you

DR DONALD G MULDER, Los Angeles Mr Chairman These have certainly been interesting and stimulating presentations I would like to comment briefly on the metabolic aspects of perfusion

As has been stated, what we should accept as an adequate perfusion is as yet unsettled It would certainly seem logical that the nearer one could come to reproducing a normal preperfusion status, the better the patient should tolerate the extracorporeal by-pass Such control is governed primarily by the composition of the arterialized blood presented to the patient and the rate at which it is delivered

Biochemical and physiological observations were made in 43 dogs before and after cardiopulmonary by-pass utilizing the University of Minnesota bubble type oxygenator, one group of 29 animals being perfused at 35 ml /kg /min , and the remaining 14 animals at 70 ml /kg / min The perfusion times were 20 minutes for each group There was no selection of animals in regard to age or body weight The results of this study may be summarized as follows

The anticipated hypotension and increased A-V oxygen difference in the low flow animals were confirmed There was also a marked metabolic acidosis in this group characterized by a drop in pH of 0 2, and a concomitant rise in lactic acid The high flow animals, on the other hand, had a drop in pH of only 0 1, and an insignificant rise in lactic acid No significant changes in pCO_2, potassium, glucose, or amino-acid nitrogen were detectable in either group

We conclude from these data that a marked hypotension and a severe metabolic acidosis may be anticipated with low perfusion rates

It is our feeling that low flow rates are undesirable and avoidable We should perfuse at flows approaching the estimated cardiac output of the anesthetized patient

DR. WILL C SEALY Durham Our interest in extracorporeal circulation has been directed toward studying the advantages of combining this technic with hypothermia for open heart surgery In the laboratory the results of more than 100 studies on the dog have demonstrated that these two technics were complementary The predicted dangers of troublesome cardiac irritability did not occur when temperatures above 27°C were used and the ventriculotomy was done under cardioplegic control This next slide is the summary of one series of experiments using this combined technic plus cardioplegia with potassium, magnesium and prostigmine It is worthy of comment that there was no difficulty in restarting the heart in either the cold or the warm group after elective cardiac standstill The one death in nine animals within the hypothermic group and the five of six in the normothermic experiment were not due to cardioplegia Conduction abnormalities after cardioplegia were of only momentary duration in either group

In experiments on dogs where extracorporeal perfusion is used, the role of any one factor in determining survival is very difficult to assess The remainder of this discussion is concerned with our clinical studies The use of this combination of methods for repair of atrial septal defects and valvular stenosis offers a better opportunity than most other operations for the evaluation of the safety of these perfusion technics The need for cardioplegia is excluded in these operations the right ventricular muscle is not damaged, the conduction tissue is avoided, and the associated pulmonary vascular changes are less pronounced In our clinic we have operated on 21 patients with these two types of anomalies Flow rates of 12 cc. to 30 cc per kg per minute were employed while hypothermia of 29°C to 32°C was used There were no complications or deaths In two of the group septum primum defects were found while in three abnormal pulmonary venous return was present as an additional anomaly As long as 24 minutes were needed for repair in some

In the repair of fourteen ventricular defects the mortality has been distressing Death occurred in six of our patients Five of the deaths occurred in patients who had systemic and pulmonary pressures that were equal while the last death was in a patient with tetralogy of Fallot in whom obstruction of the aorta was produced by the repair

almost invariably died These deaths could be ascribed to the pulmonary parenchymal changes, to what seemingly was a respiratory death Therefore, it is not surprising that the administration of sodium bicarbonate in an attempt to surmount this acidosis did not alter the survival rate

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slight fall in the pCO_2 and a progressive although not severe metabolic acidosis The precise response to the metabolic acidosis could not be ascertained The pyruvate rose slightly but not sufficiently to account for the change noted The lactic acid data were not included nor were the plasma hemoglobin values

One thing not mentioned here previously is the possibility that the red cells may continue to hemolyze following perfusion In a series of animals the plasma hemoglobin continued to increase in several instances to almost 120 mg per 100/cc. of blood after perfusion was stopped.

There are several other things I would like to mention First the control of temperature of the pump oxygenator circuit. I think this is of some importance particularly in view of the fact that full oxygen saturation of the plasma and a high oxygen tension may result in greater permeability Permeability of the blood may be such that it could result in the formation of minute air bubbles Another problem I think worthy of comment is that of bacterial contamination. During the first experiments this was thought to be a matter of considerable importance in evaluating survival perfusions in the laboratory In this group of animals twelve of twenty three tests in which contamination occurred, the animals survived. In only two of the ten in which the intestinal organisms were found were they still present twenty four hours later

The final point I would like to comment upon is that of the progressive metabolic acidosis I think it is not completely explained Presumably it can only occasionally be due to the bacterial contamination

DR HAROLD J C SWAN Rochester Minn. I think it is correct that the ideal circulation is one that does what it is supposed to do What you are trying to do in body perfusion is to supply appropriately oxygenated blood to the tissues of the whole body Under circumstances in which whole body perfusion is less than complete, there seem to me to be two possible consequences either certain areas and organs of the body still receive their total complement of blood, and therefore their needs are completely looked after and some other organs receive little or no blood and their needs are very inadequately cared for or hypoxia is generalized in relation to the degree of adequacy of the perfusion We favor the former according to Kunster As described in Dr Kirklin's presentation of this morning's session the oxygen consumption is lower that is about 110 to 115 cc per minute as compared to a normal of 135 to 140 cc and in less complete

In this group of patients there were two who had A-V block following surgery In all of these patients the heart was stopped with potassium, magnesium, and the prostigmine solution The longest period of standstill for any patient in this group was 32 minutes with extracorporeal perfusion for 55 minutes at 30 cc per kg per minute

The next slide is a summary of the arterial pH, arterial oxygen, and mixed venous lactic acid during perfusion on one patient with tetralogy of Fallot The patients were perfused at rates of 25 to 45 cc per kg, depending upon weight and were kept at rectal temperatures as low at 29°C

The next slide shows the operative data on another patient with tetralogy of Fallot Air embolus occurred before the extracorporeal circulation was started Then the heart stopped

From our laboratory and clinical studies we found that hypothermia and extracorporeal circulation were compatible A more extensive clinical trial is needed before we are certain both are necessary It is our present opinion that by using both, lower flow rates can be employed with greater safety, and therefore complicated mechanical, electrical, and electronic devices can be minimized This also allows us to use a heat sterilized plastic oxygenator prepared by our own central supply If there is an accident with some component of the system, one has a few minutes to correct the breakdown The disadvantage of cardiac irritability at temperatures above 28°C is not so important when one has the support of extracorporeal circulation and an effective cardioplegic such as potassium, magnesium, and prostigmine

The real disadvantages of this combination are the extra time needed for cooling, the difficulties in controlling the degree of coldness, and slowness of rewarming We now have, through the work of Dr Ivan Brown, a heat exchange mechanism that shows promise of allowing us precise control of the temperature during extracorporeal circulation With this instrument we hope to carry out most of the cooling with extracorporeal perfusion and in turn to rewarm the patient more rapidly at the conclusion of the procedure

DR DWIGHT S SPRENG, JR, Brooklyn I should point out that I am not now actively associated with the group in New York

This slide (figure not available) summarizes the data that have been collected on a series of dogs, averaging 17 7 kg body weight, during perfusion with a flow of 90 cc /kg /min This rate was maintained, and averaged 5 cc oxygen per kilo There was a slight rise in the pH, a

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perfusion we may have oxygen consumption reduced to 75 per cent of that value If that is so, some part of the body may not be getting quite enough oxygen If the first possibility is true, there would be a marked reduction to certain organs and not to others There are certain consequences of that which I believe are important because they may lead to erroneous conclusions Under the circumstances the venous blood oxygen saturation may not be significantly reduced even in the presence of almost completely reduced blood flow because there isn't enough oxygen in that tissue, and the tissue will go into oxygen debt If this deficit is maintained for a long time, tissue damage will result I am only speculating and I am using the words "may" and "might"

To me a mean normal arterial blood pressure seems to be a laudable objective, because with a blood pressure approaching the normal range the perfusion of all organs is more likely to be obtained than with low perfusion The characteristics of the various vascular beds differ widely, and the analogy, that sometimes it is simply the "D-C circulation," is a very general one In these terms the parameters of the situation may be drastically altered such as we have here Indeed,– the pulsatile and non-pulsatile blood flow may be of some significance too, since some of these vascular beds may be more directly dependent on these elements than others

Another point is the actual volume of flow we are measuring Dr McMillan said that his meter did not measure the back flow I think if you are going to measure effective forward flow, your meter must recognize back flow Otherwise you are not likely to get worthwhile results, and when we think of flow we must recognize the various factors, bronchial blood mostly, which must be measured, since a good bit may be going into the bronchials The actual flow may not be the volume perfused into the total body at all

DR FRANK GOLLAN, Nashville Not being a surgeon, I have used the pump oxygenator for physiological studies, and that I do not recommend or extol

We have remodeled the average bubble oxygenator in such a way that we now have a porous filter with the venous inflow with the inner volume cylinder taken out, and a temperature regulating device, Figure 86

This is the instrument, which is made of a high polymer polyester so that it can be boiled, Figure 87

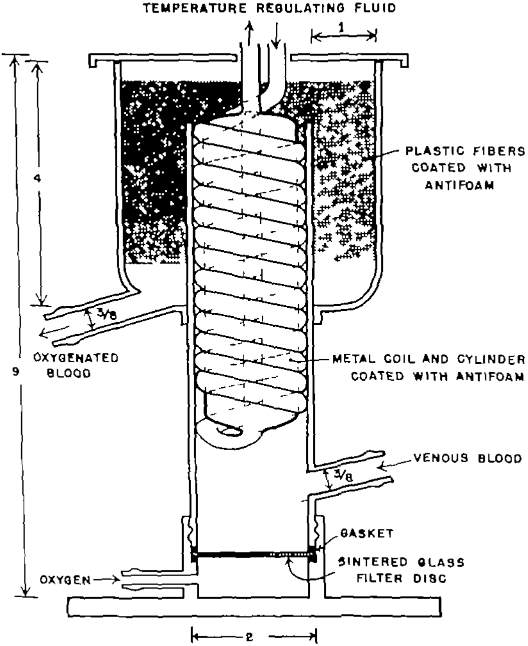


FIGURE 86 (Gollan)

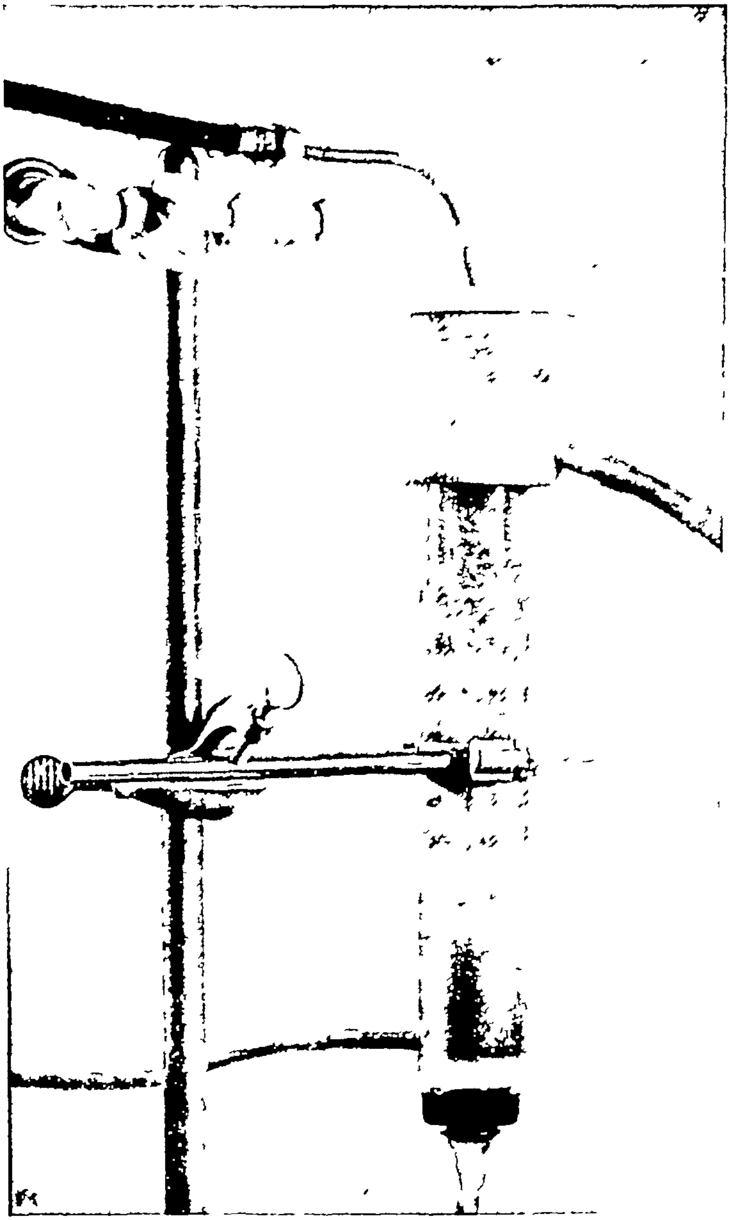


FIGURE 87 (Gollan)

Then when we perfuse—Figure 88 shows a chart of the organs we do perfuse, and we use also a type of selective hypothermia sometimes we have a difference of about 20 degrees in the body

Figure 89 shows that the heart goes slowly into arrest as temperature is reduced The motion of the heart is recorded with an open venous electrode until ventricular fibrillation occurs

Figure 90 shows the exceedingly high oxygen content in plasma of such animals below 14°C The consumption is exactly where you would expect it to be which is just beyond the point reported in the literature While I suppose this hasn t been done before I want to be the first to say that it wasn t necessary to do it in the first place These red points

SELECTIVE BODY HYPOTHERMIA DURING BLOOD COOLING

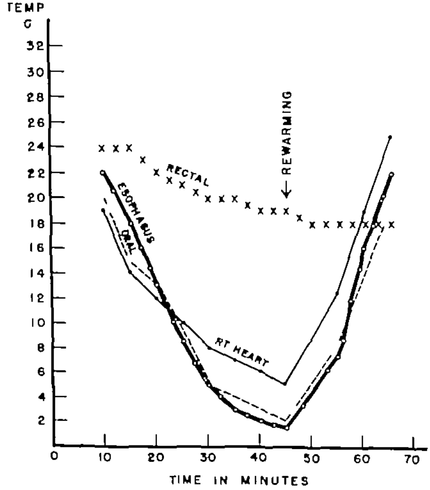


FIGURE 88

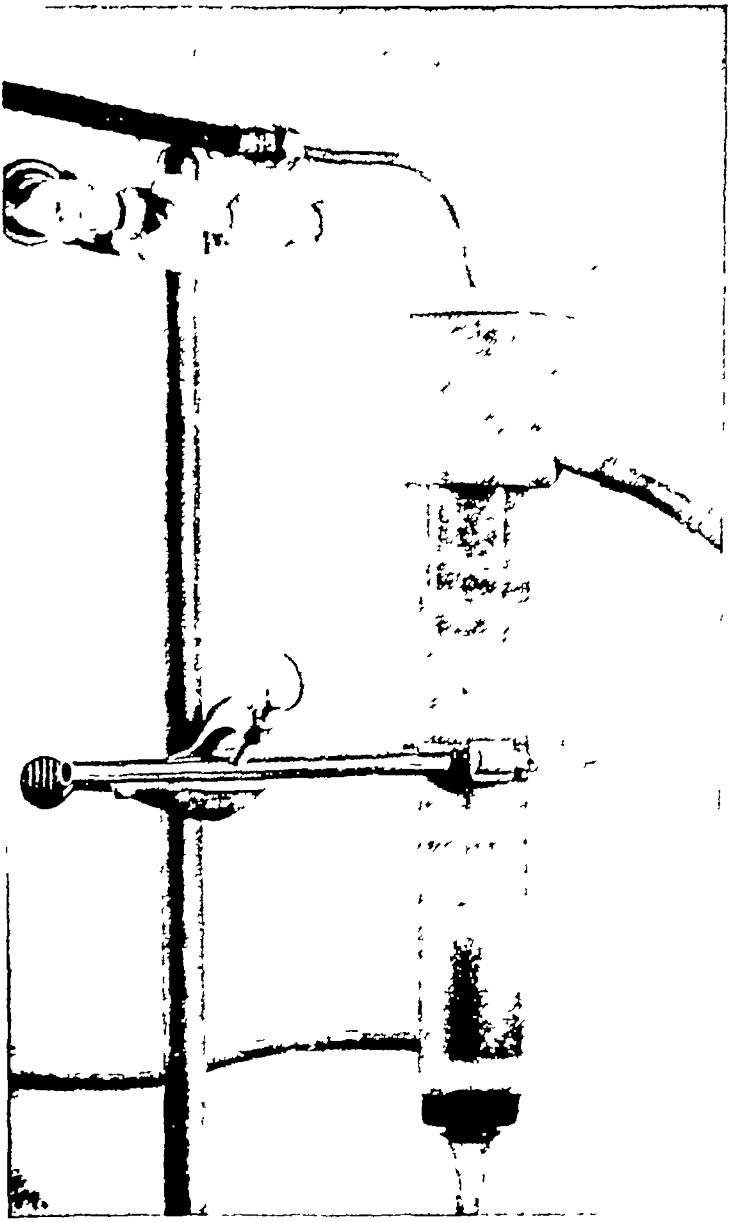


FIGURE 87 (Gollan)

accomplished with a very small and simple instrument You need cannulate only the peripheral veins the heparin level can be very low but the coagulation time much shorter as you rewarm Second, there is no danger of overloading You can overdue oxygenation This

OXYGEN CONSUMPTION AND OXYGEN SUPPLY IN SEVERE HYPOTHERMIA WITH PUMP OXYGENATOR

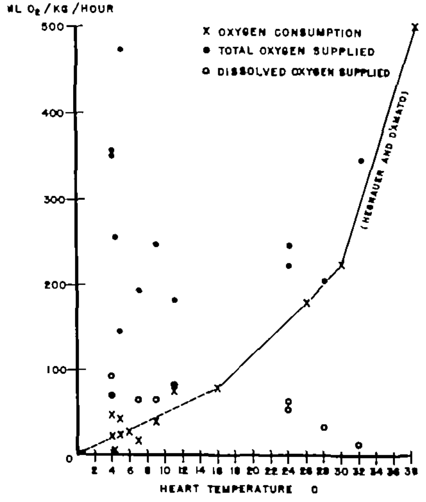


FIGURE 90

is one of the good things you can really overdo There is very little hemolysis, and no ventricular fibrillation Cardiac arrest is produced with a much smaller amount of potassium citrate and the occlusion period can be prolonged up to 4 30 PM when the government offices close

show the large amount of blood which is supplied to these animals, the total oxygen is far in excess of the total oxygen requirement The yellow dots show the total amount dissolved in the plasma which, with low temperature, goes up abruptly

From Figure 91 I suspect that the oxygen flow might go right out the top of the galvanometer

Figure 92 shows the flow when we have a venous pump system Then we can follow pretty closely the cardiac optimal amount, determined

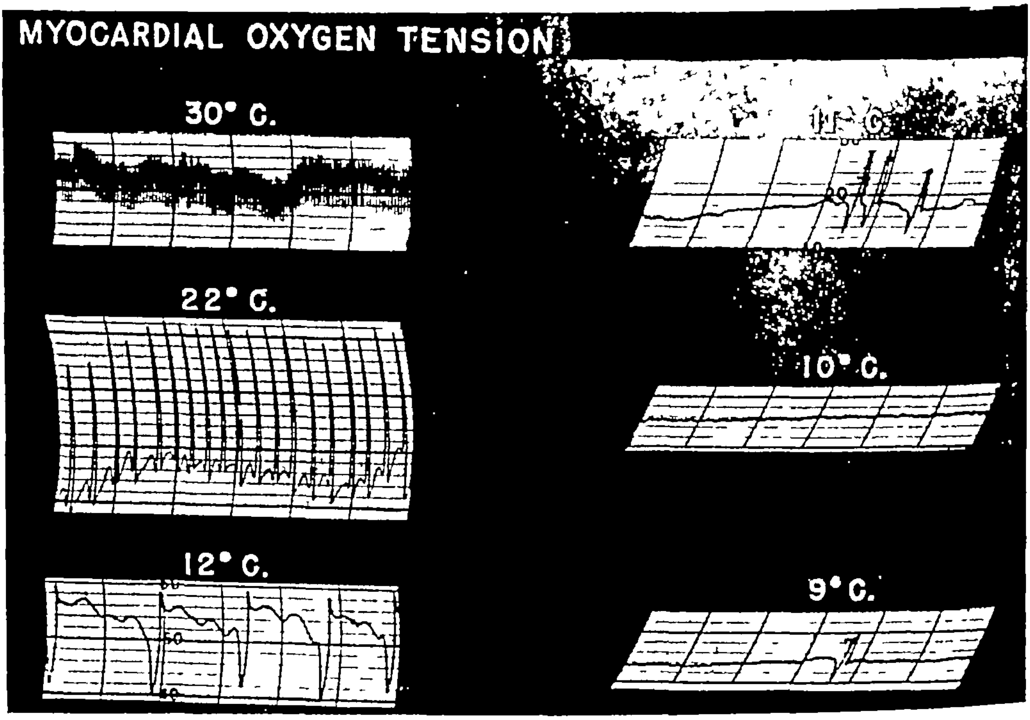


FIGURE 89

in the hypothermias used When we use the flow from the gravity pump by Bigelow, flow stays way up, and is something like 20 cc at 30°, and may be something like 15 cc at 20°C This is self-regulatory because as the animal becomes hypothermic, it cools large volumes of whole blood, or blood that is stagnating in the capillaries in a manner that is similar to the way the dog adjusts it automatically

In a study like this I do not know whether the results have any practicability

Anyhow it was interesting to me May I have the last slide?

I want just to summarize the advantages I feel there are in such procedures of oxygenation, Figure 93 First, cooling is very rapid It is

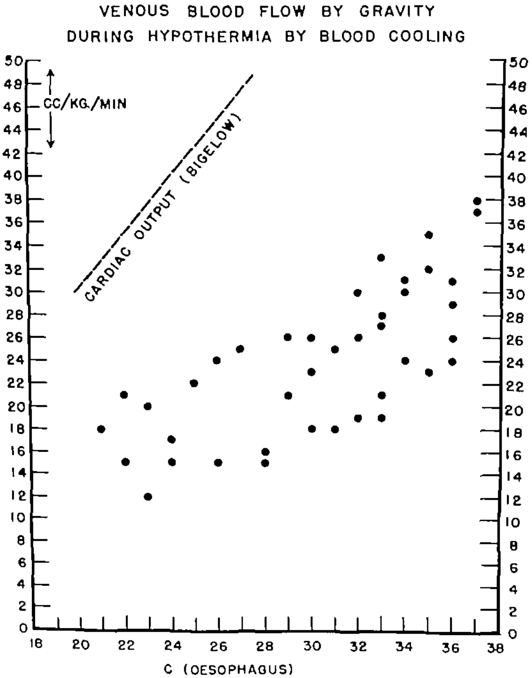

VENOUS BLOOD FLOW BY GRAVITY
DURING HYPOTHERMIA BY BLOOD COOLING
CC/KG./MIN
CARDIAC OUTPUT (BIGELOW)
C (OESOPHAGUS)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
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36
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FIGURE 92.

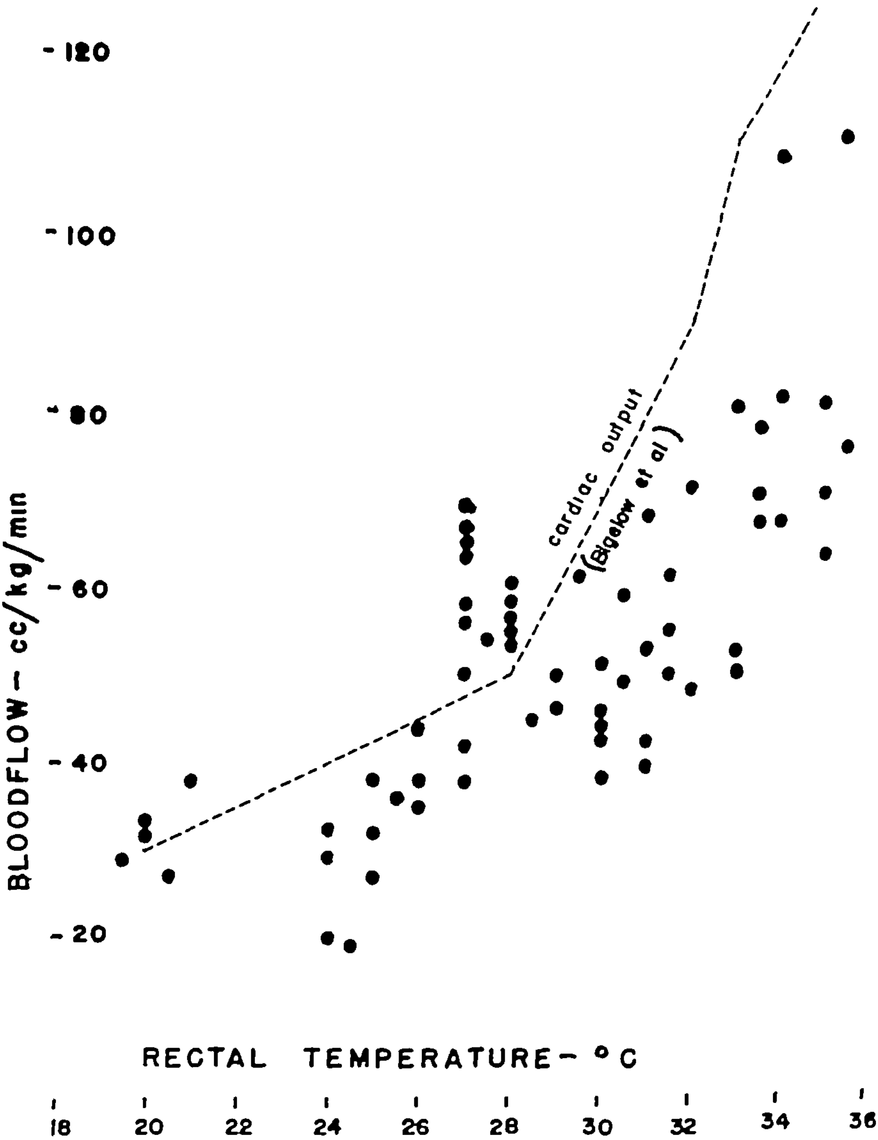

120
100
80
60
40
20
BLOODFLOW - cc/kg/min
cardiac output
(Bigelow et al)
RECTAL TEMPERATURE - °C
18
20
22
24
26
28
30
32
34
36

FIGURE 91

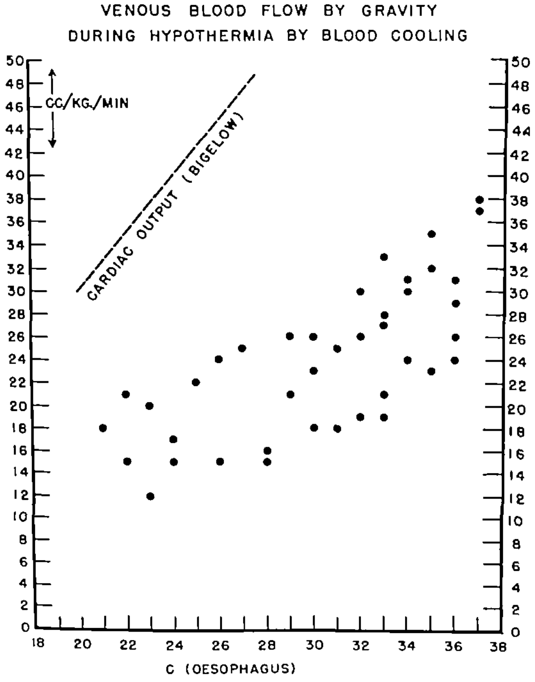

VENOUS BLOOD FLOW BY GRAVITY
DURING HYPOTHERMIA BY BLOOD COOLING
CC/KG./MIN
CARDIAC OUTPUT (BIGELOW)
C (OESOPHAGUS)

FIGURE 92.

ADVANTAGES OF PERFUSION WITH COOLED, OXYGENATED BLOOD

1 RAPID AND CLEAN
2 DIFFERENTIAL COOLING OF INTERNAL ORGANS
3 SMALL INSTRUMENT PRIMED WITH COLD RINGER'S SOLUTION
4 LOW FLOW FOR NORMAL A-V DIFFERENCE
5 CANNULATION OF PERIPHERAL VEINS ONLY
6 LOW HEPARIN DOSAGE DURING COOLING
7 NORMAL BLOOD CLOTTING ON REWARMING
8 NO DANGER OF OVERLOADING WITH FRESH, COAGULABLE BLOOD
9 LOW HEMOLYSIS
10 NO VENTRICULAR FIBRILLATION (30 mg QUINIDINE/kg)

FIG 93 (GOLLAN)

(Any inaccuracies in this discussion are due to transcript not being entirely clear [ED] *)*

DR JAMES W DOW, Boston I hope that Ian McMillan is still in the room because I am sure he will be charmed to know that, for the recording of blood flow, a Venturimeter is now commercially available, Figure 94

The slide shows the device mounted in the venous return line during heart-lung by-pass The Venturitube is bored from a lucite cylinder The included angle of the entrance cone is 20°, and that of the diffusion cone 7° The pressure taps are let into the tube just proximal to the entrance cone and at the throat These taps are adapted to the positive and negative chambers of a Sanborn differential manometer Tubing connections are tapered so that lumen is not impaired and are locked on with bushings The pressure differential created by flow is sensed by the differential manometer and recorded by any suitable system, in this case by a Sanborn polyviso with carrier preamplifier An integrating switch is necessary to prevent excessive vibration of the writing arm A tube with 1/8″ throat is appropriate for animals and smaller children A 1/4″ throat is needed for larger flows in adults

The system is stable, reliable and easy to use The expense is negligible for laboratories equipped with recording devices, particularly if the equipment includes a fluid differential manometer The tube must not be placed in the arterial line during human perfusions, since pressure falls far below atmospheric with the constriction, allowing entrance of air through any leaky fitting

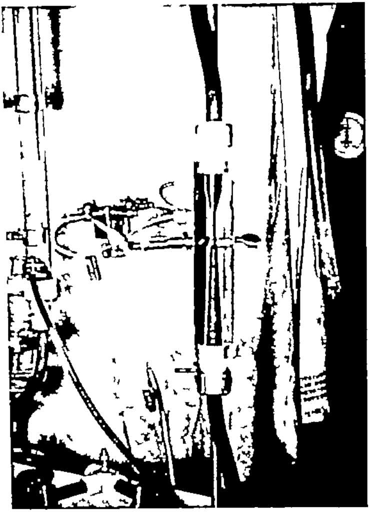


FIGURE 94 Showing Venturimeter (Dow)

DR. E CONVERSE PEIRCE, Knoxville I enjoyed the very excellent papers by Doctors King Sealy and Gollan on the use of hypothermia and the pump oxygenator I have been interested in this subject for some time

In hypothermia I think it is important to consider the various types of hypothermia. What one learns from one type is not necessarily translatable to other types For instance in external hypothermia one gets very low external temperatures and a moderately low core temperature In cooling the blood if the temperature is very low the core temperature may still be relatively high, and we must assume that these findings are due to the use of external cooling technics As a matter of fact, external cooling can approximate frostbite but to assume that it is the same thing I think is wrong

ADVANTAGES OF PERFUSION WITH COOLED, OXYGENATED BLOOD

1 RAPID AND CLEAN
2 DIFFERENTIAL COOLING OF INTERNAL ORGANS
3 SMALL INSTRUMENT PRIMED WITH COLD RINGER'S SOLUTION
4 LOW FLOW FOR NORMAL A-V DIFFERENCE
5 CANNULATION OF PERIPHERAL VEINS ONLY
6 LOW HEPARIN DOSAGE DURING COOLING
7 NORMAL BLOOD CLOTTING ON REWARMING
8 NO DANGER OF OVERLOADING WITH FRESH, COAGULABLE BLOOD
9 LOW HEMOLYSIS
10 NO VENTRICULAR FIBRILLATION (30 mg QUINIDINE/kg)

FIG 93 (GOLLAN)

(Any inaccuracies in this discussion are due to transcript not being entirely clear [ED] *)*

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Dr Allen made possible this morning Number 1 is an experiment performed on a 10 2 kilo animal with a 260 cc. flow rate The oxygen consumption was reduced from a very high rate to 55 The expected oxygen consumption was in the order of 80 cc per minute If you cool such an animal slowly by partial perfusion until the esophageal temperature is in the range of 25°C and then start a total by pass with a flow of 390 cc the A V difference is only 40° Finally the oxygen consumption in #101 was measured and was only 23 3 cc. Oxygen consumption in a normal animal (10 kg) with a total by pass the oxygen difference on cooling was 57 per cent of the basal consumption

Here are further data from that experiment We start with 37 4°C with 230 cc flow per minute flow which means that seven kilo calories were extracted from the dog in thirty four minutes In a 10 kilo cooled animal there are 10 kilo calories Therefore it should equilibrate after cooling at about 30°C although the esophageal and heart temperatures fell to 24°C Presumably the brain, liver and kidney were in the same range of temperature

I do not maintain that this approach is going to have any future but I do feel that there is a necessity for using low flow rates in humans as presently practiced when one combines hypothermia with low flow rates and that these combined procedures will produce considerable metabolic improvement.

DR. STANLEY J SARNOFF Bethesda I have only one comment to make really To simplify the future communications in this area I wonder if it might not be a good idea for the people presenting data on flow rates to specify how their impressions about it were accumulated. Was it obtained with a precalibrated pump was a flow meter used, and what type of flow meter? It is simply that if someone else were attempting either to imitate or to see different elements such a person would have more precise knowledge about the comparative figure they are trying to imitate

One other minor comment Mr Chairman In search of a new type of pump I have tried to use my idea of what is a team perspective have improvised about the nature of the development of this art, and have done some extrapolating as to where this might lead

Just a word about some of my ideas Especially Dr Sealy indicated that the cool boys might be getting hot again That hypothermia might not be too remote is a real possibility One might even get a little more concrete and mention an analysis that an observer is working on The work was done by Stanley Brockman and Blalock s group Brockman

Figure 95 simply shows what Dr Gollan has already shown, but we don't cool to such an extent as he does The rate of fall in temperature of the kidney is the same range as the heart, brain and esophagus The skeletal muscle and rectal temperatures fall relatively slowly on cooling, while the other organs at a high flow cool rather quickly It is easy to understand why this happens if one looks at the basal flow of the organs which are only a little more than the total weight of the

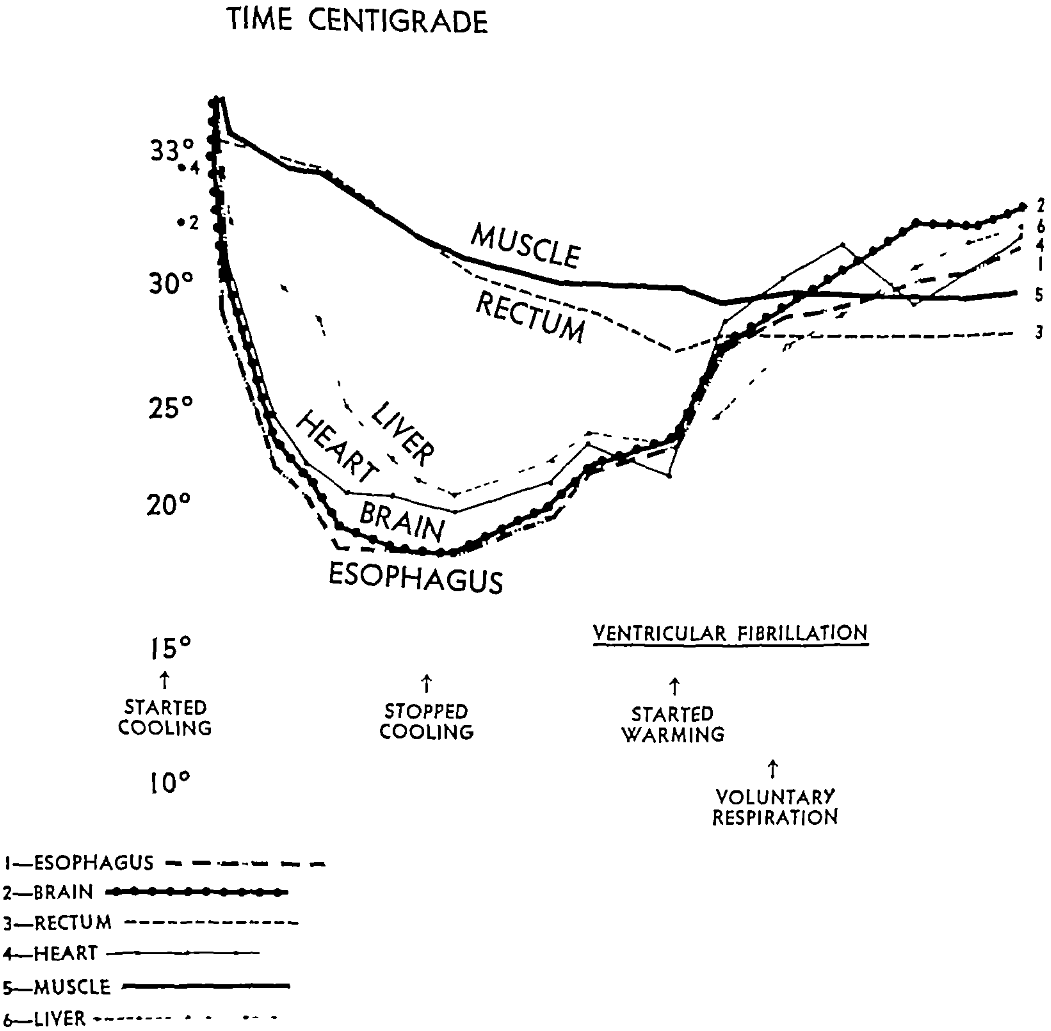


FIGURE 95

dog It is readily seen in which of the vital organs of the dog the temperature falls very quickly with low flow rates

Now for the sake of comparison I have made a little table which

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The lucite-tube and nylon adapters may be obtained from the Olson Manufacturing Company, Ashland, Massachusetts

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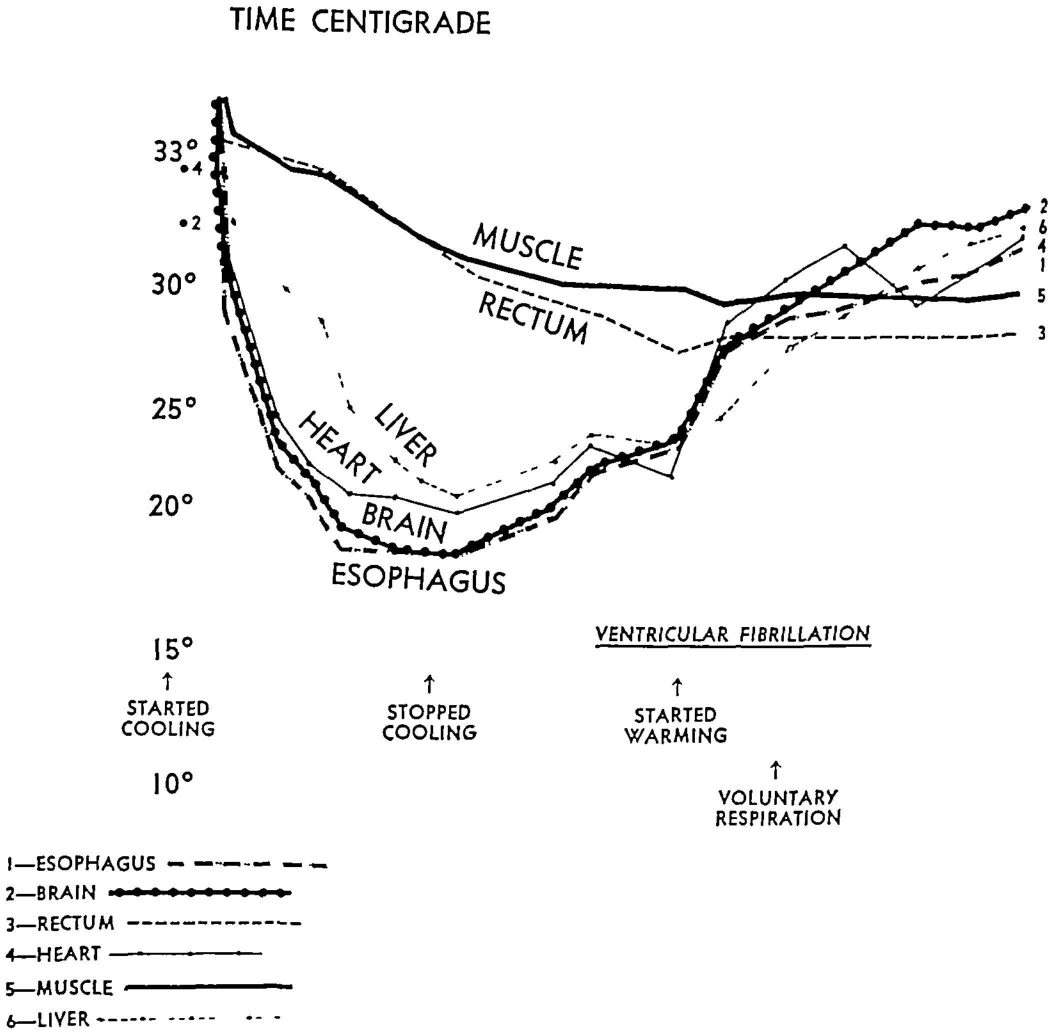


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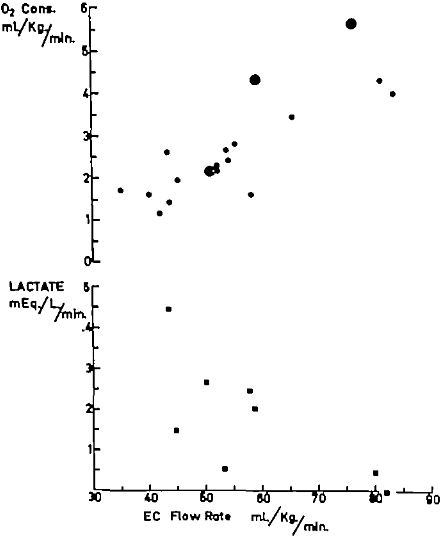


FIGURE 98

before and after extracorporeal circulation Figure 98 We calculate it as being due to a very great difference in flow rate, and we see with increasing flow rate there is increased oxygen consumption approximating controlled values at around 100 cc. per kilo We have used preperfusion oxygen consumption as the control. We did the same thing in 10 dogs before extracorporeal circulation to diminish cardiac output by occluding partially the pulmonary artery and then calculated the cardiac output according to the Fick principle You see the same thing with a decrease in cardiac output and there is a decreased oxygen consumption of the duration of extracorporeal circulation This is without extracorporeal circulation and that might be the cause of the difference of cardiac work

asked me to help analyze a series of 20 experiments he did there, and he was apparently of a mind that he knew as much as Bentall, although he had by no means the experience that Bentall has, namely that simplification is very greatly desirable He learned the hard way that the pump oxygenator is difficult to regulate, and he thought the easiest thing was to eliminate it, which he has attempted to do What he has done is to put a cannula in the left subclavian artery, and at 29° to close the cannula, and to use mecholine arrest Instantly blood was perfused into the left subclavian and the carotids He had an oxygen flow from 30 to 52 with ventriculotomy or aortotomy The analysis of this study to which I readily acquiesced, was rather interesting to me

In one of the twenty dogs he did a complete cardiac block for 30 to 52 minutes at 29° This dog presented transient ataxia for one day after operation The overall mortality was this Out of the twenty dogs, twenty dogs survived I thought that was rather impressive *(Any inaccuracies in this discussion are due to transcript not being entirely clear* [ED] *)*

DR AKE SENNING, Stockholm, Sweden I am going to show three slides

In the first slide, Figure 96, we have tried to show oxygen consumption in relation to flow rate These are the first 18 patients we operated upon On this slide you see immediately the per kilo, and the extracorporeal blood rate in milliliters per kilo body weight per minute You can see that as you increase the flow rate you increase the oxygen intake which is in a range of 20, 40 and 60 At the same time we measured in nine patients the increase in lactic acid, before, during and after extracorporeal circulation Here is increased lactate in milliequivalents per minute in the extracorpeal period which has been of different lengths With low flow, you see there is increased lactate, but with a high rate there has been no increase in lactic acid

Shown in Figure 97 are the results from three patients in whom we did oxygen consumption before anesthesia, after anesthesia and during extracorpeal circulation, and we had a difference, first of 82, and 50 and 65 With 82 cc per kilo per minute with the same oxygen during, after and before extracorporeal circulation, here there is a great difference in the rate of oxygen consumption These are not relatable to the duration of extracorporeal circulation

With Murray Anderson of Buffalo, we did a laboratory experiment on dogs to see the correlation between blood oxygen and the rate of flow At first we tried before and after anesthesia experimentally and

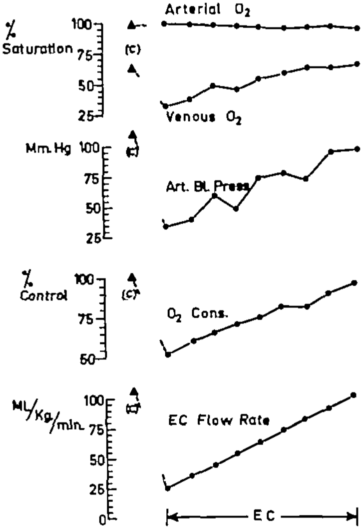

% Saturation
100
75
50
25
(C)
Arterial O_2
Venous O_2
Mm.Hg
100
75
50
25
Art. Bl. Press.
% Control
100
75
50
O₂ Cons.
Ml/Kg/min.
100
75
50
25
0
EC Flow Rate
EC

FIGURE 99

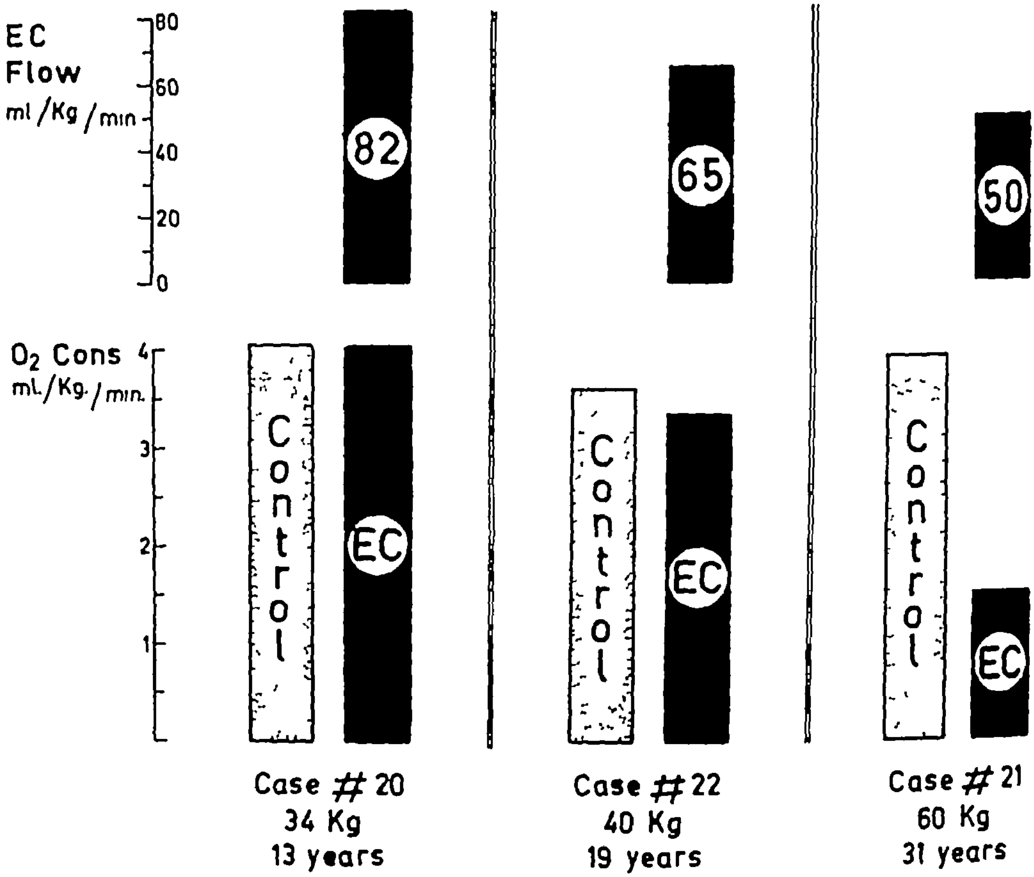


FIGURE 97

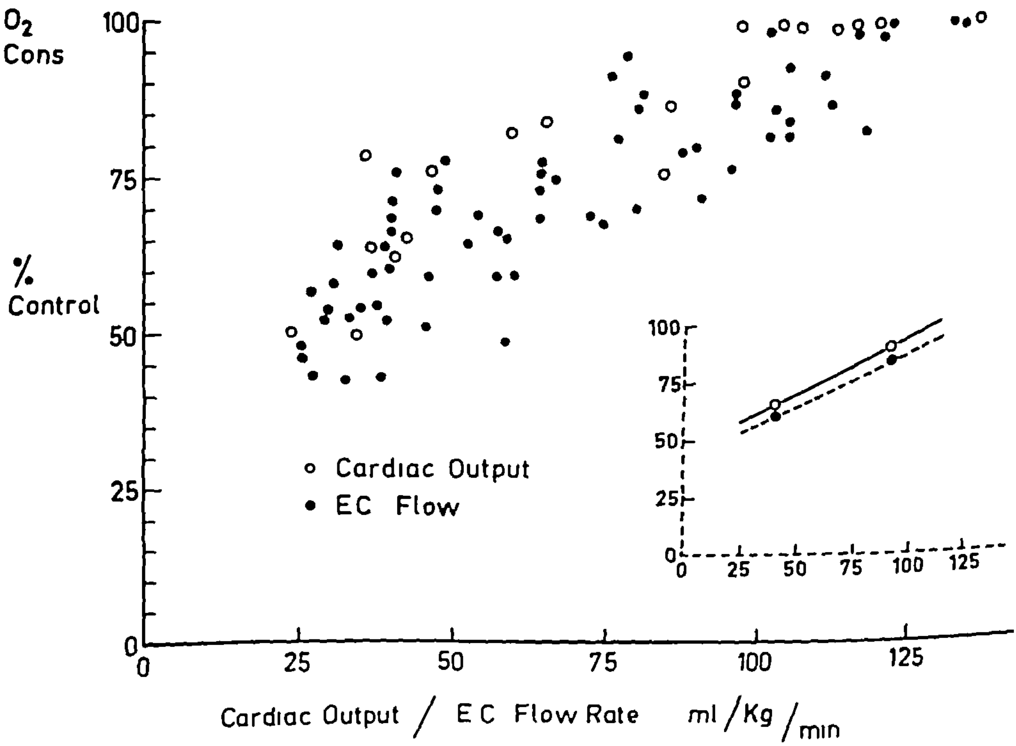


FIGURE 98

THE EFFECT OF PERFUSION ON ORGANS

SECTION III

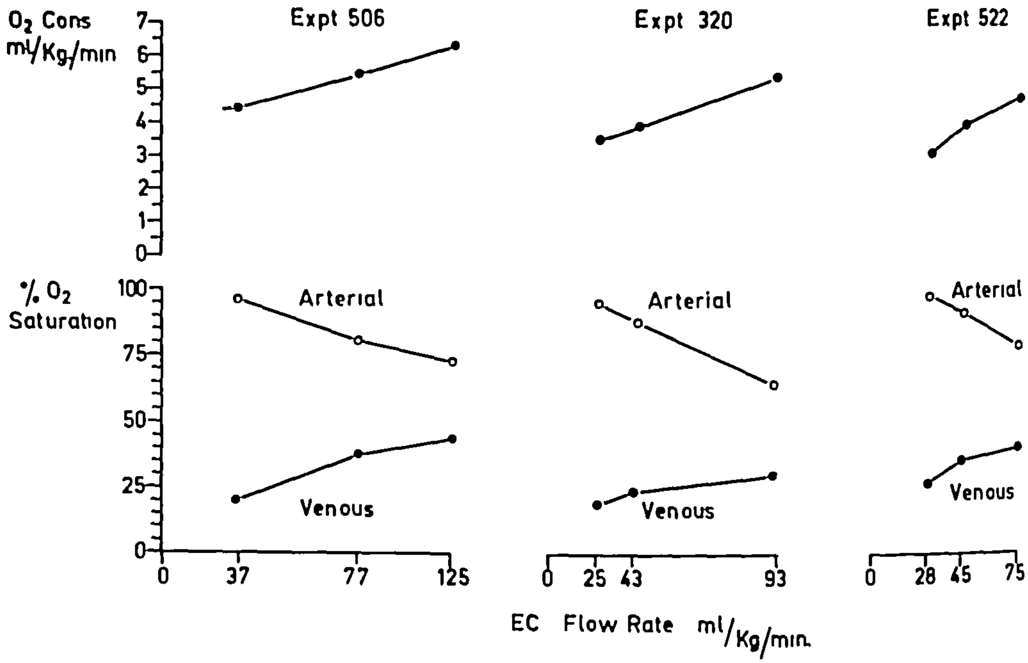


FIGURE 100

In Figure 99 we have plotted the flow rate with the oxygen consumption and compared it with the control values as they were before extracorporeal circulation There are marked high angles here, and with increasing flow rate, the oxygen consumption goes up about 100 per cent, the same as before perfusion The arterial blood pressure goes up, but it doesn't reach preperfusion levels The arterial-venous difference is more or less the same as it was before extracorporeal circulation

We made an experiment on animals who were too large for oxygenators, Fig 100 We have the oxygen consumed and the arterial saturation, oxygen saturation decreased, and at the same time the venous saturation increased What happened is that the oxygen consumption goes up in all three experiments

PROBLEMS AND QUESTIONS ON COAGULATION OF BLOOD ARISING FROM THE USE OF EXTRACORPOREAL CIRCULATION PUMPS AND OXYGENATORS

By

J GARROTT ALLEN, M D

I. SOME FACTORS AFFECTING IN VIVO COAGULATION OF BLOOD AND THE MAINTENANCE OF ITS NORMAL FLUID STATE

ANY EXTRACORPOREAL circulation may occasionally result in disaster from uncontrollable hemorrhage The nature of this bleeding diathesis is poorly understood because several of the clotting components may be affected singly or in combination Moreover it must be acknowledged that our theories on coagulation exceed our facts and until such time that knowledge is advanced as far as speculation, we will be unable to interpret adequately the total picture

Most studies in the field of blood coagulation during the past 95 years have been *in vitro* in character Remarkably few attempts have been made to study coagulation in the living preparation While neither approach is simple nor free from criticism the hemorrhagic diathesis associated with extracorporeal circulation pumps and oxygenators is extraordinarily difficult to evaluate by the *in vitro* technic alone With viviperfusion we are confronted with the necessity to examine blood and its coagulation under both of these circumstances particularly by suitable *in vivo* methods

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We have arrived at a stage in the development of cardiac and

vascular surgery which is considerably in advance of our knowledge of blood coagulation, despite the large body of data derived from clotting studies under the special *in vitro* conditions the coagulationists have employed In the minds of most who have worked on blood clotting, the years between 1861 and 1942 constitute the golden era of coagulation The first observations in this period were by Alexander Schmidt of Dorpat who began his studies in 1861 About the time of Schmidt's retirement from the field, William Howell of Baltimore entered and remained actively engaged as its leading investigator until his death in 1942 These and other investigators, too numerous to detail, were able to establish the *in vitro* function of the following major components of coagulation. platelets, prothrombin, fibrinogen, fibrin, clot retraction, fibrinolysis, the calcium ion, heparin, the various accelerators and inhibitors of coagulation, and vitamin K In addition, the development of the fractionation technics for the proteins of plasma has permitted the study of the clotting components in isolated *in vitro* systems as well as provided us with the therapeutic concentrates of fibrinogen and antihemophilic globulin If we were to add to the 80 years in which Schmidt and Howell worked, the 15 which have elapsed since Howell's death, we have spent nearly a century on the *in vitro* approach to coagulation Admittedly, the *in vitro* technics have yielded an abundance of very fruitful information However, in the use of such laboratory methods for *in vitro* study, we have seldom touched upon the problem of abnormal clotting or abnormal hemorrhage in the living We know little of the real mechanism of the bleeding in any hemorrhagic diathesis regardless of its cause, including that of the central theme in this conference, *i e*, extra-corporeal circulation, pumps and oxygenators The last serious attempts to study the clotting mechanism in the living preparation were those of the surgeons, John Hunter, Astley Cooper, and Joseph Lister, all prior to 1863

We cannot yet answer the two important questions which have motivated most of the studies on coagulation from *day one* Why does blood clot when it is shed, and by what mechanism is the circulating blood able to maintain its fluid state in the normal circulation? Our understanding of extracorporeal coagulation exceeds considerably that of the *in vivo* clotting mechanism, our

knowledge of the clotting functions of the various components of coagulation in isolated systems which seldom if ever exist in life is advanced beyond reasonable hope that similar achievement will obtain in our life time on the coagulant properties of so "crude" a substance as whole blood Perhaps a renaissance of the crude approaches of Hunter Cooper and of Lister at this time would prove fruitful and provide valuable information to our current questions relative to the causes of the bleeding syndrome as well as the troublesome problem of fibrin deposition encountered occasionally in the use of extracorporeal circulation with or without pumps or oxygenators In fact the introduction of viviperfusion technics cannot be thoroughly studied in the absence of experimental designs that include methods for the study of the clotting mechanism in whole blood in the living preparation However many of the *in vitro* technics present and past are applicable to the pump-oxygenator problems in a limited way

Let us first examine the theories of blood coagulation in relation to the hemorrhagic diathesis and the intravascular coagulation which may complicate viviperfusion It is soon apparent that these *in vitro* concepts of coagulation do not necessarily apply to our pump-oxygenator problem or for that matter to that of any hemorrhagic or clotting disorder occurring in man We might first examine these theories as they have generally been interpreted to explain the fluid state of the circulating blood during normal life Most, if not all theories have presumed that blood does not clot in the normal circulation because the major components of coagulation circulate only as inactive precursors and that activation requires some form of trauma to initiate the clotting mechanism This concept may not be correct at least in its literal sense For example one of the simplest of all theories that which Morawitz advanced in 1904 assumes the clotting mechanism to be dormant until "triggered" by some form of trauma. From his theory and most of those which followed, it is presumed that the circulating blood in the normal individual has no tendency to clot unless circumstances develop which initiate a breakdown of tissue especially those of the blood vessels or those which induce platelet lysis Most assume that lysis of platelets or the breakdown of other cellular components release from their intracellular substance a material which elaborates

a thromboplastic agent in the circulating blood. The thromboplastin generated then converts "inactive" prothrombin, in the presence of the calcium ion, into the potent coagulant—thrombin. The latter in turn transforms soluble fibrinogen into the fibrin clot.

We do not question this reaction, but our laboratory for some years has entertained considerable doubt that the clotting mechanism is inactive in the normal circulation.[1] In fact, we believe it to be normally engaged in the prevention of hemorrhagic states as well as in the avoidance of serious intravascular clotting. As knowledge has developed, it is apparent that these reactions are a function of accelerators as well as of natural inhibitors, most of these can be demonstrated *in vitro* under appropriate conditions. Moreover, we see no evidence for the existence of a force or an agent, including heparin, in the normal circulating blood which possesses sufficient power to inhibit clotting completely. Furthermore, the concept of a dynamic coagulation is in harmony with those of most biochemical or physiologic reactions occurring within the body under normal circumstances. Just as these reactions normally proceed in equilibrium, or as ones of homeostasis, under basal conditions and are capable of acceleration or retardation under non-basal conditions, we believe the normal clotting mechanism is engaged in continuous activity normally to prevent spontaneous hemorrhage on one side of this equilibrium and intravascular clotting on the other. We have examined our thesis to discover experimental or clinical evidence that blood coagulation is not the dynamic or homeostatic process we contend. Instead of contradiction, our data tend to strengthen our thesis, however, we must admit that many untested facets exist and that in at least one of these, we see no very obvious means of exploration. While we believe that intravascular clotting must normally function continuously to prevent the spontaneous occurrence of exsanguinary hemorrhagic diathesis, we have not yet been able to demonstrate how such hemorrhagic catastrophes are normally prevented. We are of the opinion that the bleeding and clotting abnormalities associated with extra-corporeal circuits, oxygenators and pumps will be more easily understood if one bears in mind the evidence that coagulation is a dynamic mechanism, instead of pursuing the previous beliefs, implied or stated, that coagulation is

only a potential activity of blood In support of the homeostatic concept the following observations are presented

A Clinical Evidence of a Dynamic Coagulation

1 *If platelets* are not actively engaged in the prevention of *spontaneous bleeding under normal conditions* how can we explain the benefit derived from restoration of the platelet count in thrombocytopenic purpura by splenectomy or the transfusion of platelet concentrates? If platelets play no role normally in the prevention of bleeding their complete absence should not give rise to a spontaneous and fatal hemorrhagic diathesis except when trauma occurs if the previous theories are correct

2. *If prothrombin* is inactive unless activated by thromboplastic substances which only can be elaborated under conditions of trauma or blood shed how can we account for the abnormal bleeding syndrome in patients with severe prothrombin deficiency or its prompt correction when the normal range of prothrombin is re-established by vitamin K administration or the transfusion of large quantities of freshly prepared plasma? This too is not explained unless one is willing to accept the dynamic role of coagulation as a normal mechanism essential to life

3 *If fibrinogen* is normally inactive as previously maintained why does its absence from the normal circulation lead to serious or fatal spontaneous hemorrhage when uncorrected? *Why should the transfusion of fibrinogen quickly control the* bleeding tendency in patients in whom this is the only abnormality present? One may examine in this same light the clinical role of the naturally occurring secondary components of coagulation both the accelerators and inhibitors the answer again seems to be the same—dynamic roles for all

These clinical syndromes and their response to the treatments mentioned are established facts They are syndromes which can be reproduced in the living experimental animal by anyone However to accept them as categoric evidence in favor of the dynamic theory is to deny one who may be curious the pleasure that comes from the use of the scientific method and its application to physi

ology as well as to many fields of clinical medicine and surgery Thus, we have examined the dynamic theory in the laboratory by several technics The results obtained appear to support our contention and may also account in part for some of the disorders of coagulation encountered in the use of the extracorporeal circulation, the pumps and the oxygenators, discussed yesterday

B. Experimental Observations on the Dynamic Role of Coagulation in vivo

If coagulation is dynamic, then we should expect the rates of turnover of the major clotting components to be fairly rapid Indeed, studies suggest that they are

1 When homologous *concentrates of platelets* are transfused in quantities sufficient to restore the platelet count to normal in the dog rendered thrombocytopenic by exposure to total body x-radiation, bleeding promptly ceases Within less than 36 hours, however, the pretransfusion thrombocytopenic state recurs and bleeding may resume This same rapid disappearance of transfused platelets from the circulation is also observed in the normal dog given enough homologous platelets by transfusion to double their normal concentration in the circulating blood [1]

2 *Prothrombin concentration* and its activity lend themselves even more readily to experimental study In the dicumarolized, prothrombin-deficient dog or man, the transfusion of large amounts of freshly prepared canine or human plasma restores immediately the prothrombin concentration and activity to normal Again, however, twenty-four to thirty-six hours later, the pretransfusion reduced level of prothrombin activity reappears as well as the hemorrhagic syndrome [1]

One can also study the rate of prothrombin elaboration Thus, we can examine fairly well the rates of elaboration and destruction of prothrombin activity to determine whether these are in equilibrium If the liver is capable of the manufacture of prothrombin, the administration of suitable preparations of vitamin K will restore the level of prothrombin activity to normal within twenty-four to thirty hours results which compare favorably with its rate of destruction Under these circumstances, it appears that

the rates of production and destruction of this clotting component are fairly well synchronized

3 The acute depletion of all *coagulable fibrinogen* from the circulation of the dog requires more drastic technics Yet the technics we have used simulate the conditions that may occur in the course of the improper use of extracorporeal circulation and pump oxygenators To this extent the following observations appear relevant and valid

Slow intravascular coagulation with complete disappearance of coagulable fibrinogen and the activation of the fibrinolytic systems can be achieved in twenty to thirty minutes by careful intravenous administration of either a thromboplastic material or thrombin Minute clots can be detected microscopically in the capillaries of most organs if the animals are sacrificed promptly to avoid the dissolution of these clots by the activation of fibrinolytic enzymes The circulating blood remains incoagulable for six to ten hours before any coagulable fibrinogen reappears The normal concentration of fibrinogen is re-established ten to fourteen hours later or eighteen to twenty two hours after the infusions of thrombin were completed

The rapid intravenous administration in dogs of activated concentrates of human fibrinolysin will destroy all coagulable fibrinogen within a minute or two after injection The fibrinolytic activity of the circulating blood can be detected for three to six hours After this period of time coagulable fibrinogen reappears reaching its pretransfusion levels within eighteen to twenty four hours The normal rates of production and destruction (metabolism) for circulating fibrinogen may be estimated by tracer technics using either C^{14} of S^{35} It is also possible to establish values for similar functions of prothrombin by these isotopic methods We found the turnover rates of fibrinogen and prothrombin when estimated by tracer methods to be in reasonable agreement with those we obtained by the biologic methods described above Thus we have concluded from our clinical and experimental studies that the circulating blood is normally engaged in the prevention of spontaneously occurring hemorrhagic disorders that almost certainly otherwise would be incompatible with life

The dynamic theory of coagulation raises more questions than it can settle at this time. The foremost questions are: How does a dynamic coagulation maintain the integrity of the circulation? By what mechanism(s) is exsanguinary spontaneous hemorrhage normally prevented? Is the pathophysiologic end result in thrombocytopenic purpura the same as that encountered in prothrombin deficiency or in afibrinogenemia? We have no answers.

However, if the clinical pattern of each of these hemorrhagic syndromes is any criterion, it seems likely that platelets function differently than prothrombin and/or fibrinogen in the prevention of abnormal bleeding. The petechial nature of the bleeding syndrome of thrombocytopenia is not shared clinically by patients with depletion of prothrombin or fibrinogen provided the platelet counts remain normal. However, the tendency for the more extensive extravasations which characterize the hemorrhagic syndromes of hypoprothrombinemia and afibrinogenemia are also seen in many with the fatal or severe hemorrhagic diathesis of thrombocytopenia, too.

If we are to explain the prevention of any spontaneously occurring hemorrhagic syndrome, one of two potential possibilities should be explored experimentally and, when possible, clinically. First, we are apparently forced to the probability that one of the important normal functions of the clotting mechanism is directed toward the smaller blood vessels to prevent an otherwise uncontrolled tendency to bleed. This part of our thesis offers the only tenable explanation of spontaneous occurrence of hemorrhage in the clotting abnormalities under discussion. The clinical and pathologic characteristics of these syndromes suggest the weakest link in the vascular chain to be the small venules and capillaries. Seemingly, platelets, prothrombin, and fibrinogen contribute directly or indirectly to the structural integrity of these vessels. Is it possible that platelets normally spend themselves in part by "plugging" the intercellular potential spaces of these small vessels, particularly the capillaries? We have searched microscopically for such evidence *in vitro* and *in vivo* but alas, without success. Is it possible that some product of platelet metabolism affects the intercellular ground substance or "cement"? We simply do not know.

It may well be that one of the products of the normal metabolism of fibrinogen is fibrin and that fibrin normally coats the surfaces of all vessels including the smaller one This is possible but we do not know that it does occur We do know that there is a coating on the surface of the intima, but we do not know its composition nor its function The ordinary methods of microscopy have not been very helpful in this respect nor have those of histochemistry that we have employed to date On the other hand the normal function of the fibrinolytic system remains to be explained Were fibrin in some form normally deposited along the intimal surfaces it may be that the fibrinolytic systems serve as a "pipe cleaner" to prevent the eventual total occlusion of vessels by this coating material especially were it eventually shown to be fibrin It is well known however that in extremes of fibrinolytic activity some of the other plasma proteins are also attacked by these enzymes including prothrombin and even platelets [1]

Acceleration of fibrinolytic activity may occur in several ways At least one of these may account for the increase in fibrinolytic activity that is occasionally reported as a contributing cause to the hemorrhagic diathesis of extracorporeal circulations of the types described yesterday The mere presence of a thrombus of blood and fibrin appears to stimulate the rate of activation of fibrinolysis from its precursor—profibrolysin It is also possible the thrombus or its associated thrombin or thromboplastin inactivates the naturally occurring inhibitor of fibrinolysin—antifibrinolysin Normally antifibrinolysin is abundantly present in blood

I have been somewhat hesitant to present so radical a departure from the usual views on blood coagulation especially before this audience My decision to do so is necessitated by the failure of other theories to explain satisfactorily what we as surgeons observe in the living patient Moreover the few facts we have at our disposal, fit much better into a dynamic coagulation than into those theories of the past A fresh point of view even if eventually proven incorrect may at least force those who hold differing views to provide the necessary *in vivo* evidence to solidify their position It will also force us to examine our own concepts by the development of new methods and the accumulation of much more data.

POTENTIAL AND ESTABLISHED HAZARDS THAT MAY BE ENCOUNTERED IN EXTRACORPOREAL CIRCULATION

What happens to the clotting mechanism in the course of extracorporeal circulation depends upon how extensively the dynamics of coagulation may be accelerated while the circuit is open, the character of the circuit and its use Some of the papers presented yesterday and this morning disclose that, as experience with the use of pump-oxygenators accumulates, many of the mechanical defects are reduced or corrected, and that the changes in blood coagulation are less frequently observed and are less severe Yet, to some extent, abnormal bleeding and coagulation continue occasionally to present serious problems The causes of this type of hemorrhage are partly explained on the basis of the following observations

The importance of smooth, non-wettable, and clean surfaces throughout the circuit have been mentioned by many In Figure 101 is shown the effects of a rough connection in an otherwise clean and fairly smooth surface of Mayon tubing Both pieces of tubing were filled to five-sixths of their volume with human blood containing 15 mg of heparin per liter The ends of the tubings were then joined and held in place by the rubber collar shown in this figure These tubes were then rotated continuously at 60 rpm at 30° C Platelet counts and determinations of fibrinogen were made prior to this test and at the end of fifteen and thirty minutes of rotation in each tube The results are presented in Table 1

While the platelet count fell in the blood of both tubes, the drop was much greater for the blood contained in the tubing in which one end was forced inside the other to complete the circle In the tube in which the ends were cut smoothly and held in apposition without a rough surface, the decline in platelet counts was less severe The concentration of fibrinogen, after neutralization of heparin in these samples by the same milligram weight of protamine per liter of heparin, was not materially changed However, the clottting time after the addition of protamine was prolonged in both tubes compared with that of the controls

Another hazard in extracorporeal circuits that may be overlooked is the anti-heparin effect of platelets If a fairly pronounced

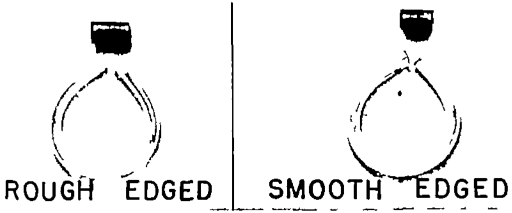


Fig. 101 Photo on left is of Mayon tubing which when filled to about 85% of volume with heparinized blood was joined in a circle with one end forced into the other giving the "rough" edge The tube on the right was joined by apposition of smooth edges held by exteriorally placed rubber collar After rotation 15 and 30 minutes platelet count was distinctly lower in the "rough" tube, see Table I

fall in the platelet count occurs for any reason the quantity of heparin required to maintain autocoagulation is reduced almost exponentially This fall may increase the extent of bleeding from the same quantity of heparin and therefore require an increase of protamine to counteract the effect of the anticoagulation from heparin.

Should severe thrombocytopenia with uncontrollable bleeding be encountered in the course of an extracorporeal circulation how can this be counteracted? To attempt the restoration of platelets by the transfusion of freshly drawn heparinized whole blood transfusions collected in plastic bags offers little benefit Here we encounter a problem similar to that of the patient with

TABLE I

Platelet Counts Per c mm. of Heparinized Blood Aliquots from Same Sample Before Rotation and Bubbling Effect 15 Minutes and 30 Minutes Later, see Fig 1

Control	*460 000*
After 15 minutes rotation	
a Smooth Seal	424 000
b Rough Seal	374 000
After 30 minutes rotation	
a Smooth Seal	339 000
b Rough Seal	216 000

severely reduced concentrations of sodium, chloride, etc , when we attempt to restore his electrolytes by the infusion of isotonic saline, it may be necessary to administer dangerous quantities of water in order to provide enough salt at the 0 85 per cent concentration To overcome this problem, we generally employ hypertonic fluids of 3 to 5 per cent saline, thereby reducing the quantity of water required The same or a greater danger of overload exists when we attempt to correct severe thrombocytopenia by the administration of enough blood to replace the quota of normal platelets Our only hope is to transfuse small quantities of platelet concentrates When properly prepared, the quantity of platelets from 10 to 15 units of blood can be transfused in less than 500 ml of plasma But this is a transfusion request that few blood banks can meet as an emergency procedure Therefore, it is better to avoid the sticking of platelets to the surfaces of an extracorporeal circuit, being certain that smooth, non-wettable surfaces are used throughout and that coagulation is prevented by heparin while the circuit is in use

Another consideration in the avoidance of the hemorrhagic diathesis after closure of the circuit is the quantitative relationships that exist between heparin and protamine sulfate The protamine that we have employed *in vitro* will neutralize heparin quantitatively in a ratio by weight of 1 to 1 Protamine performs even more effectively *in vivo* when administered by vein, except when thrombocytopenia also is present Then more protamine is required One must bear in mind, however, that the rate of destruction of protamine when injected intravenously exceeds that of heparin Therefore, occasionally a second infusion of about half the initial amount of protamine may be required about 2 hours later [3]

Protamine does have an anticoagulant action of its own when given in large excess We have not encountered this action when less than 2 mg of protamine per kilo of body weight has been administered

Our studies on prothrombin activity and its utilization does not disclose any abnormality, provided extensive intravascular coagulation is prevented by heparin, and that fibrinolysis does not become an acute problem If coagulation does occur or high titers

of fibrinolysin do develop prothrombin also may be consumed or digested rapidly This proteolytic system can digest prothrombin to the point of depletion [1]

Fibrinolytic enzymes may be activated or their rates of activity accelerated by one of several methods In this report we are concerned primarily with the accelerated rate of fibrinolytic activity by intravascular coagulation If clotting becomes a serious problem the fibrinolytic system may be activated very quickly and very high titers may occur If one attempts to simulate the extremes that can occur from the improper use of an extracorporeal circuit, with or without a pump and an oxygenator by the slow intravenous infusion of small quantities of thromboplastic material or thrombin in the dog, minute emboli of fibrin and of agglutinated platelets are deposited throughout the capillary beds of all organs Survival is possible but neurologic sequelae with evidence of brain damage not dissimilar from that attributed yesterday in this conference to oxygen intoxication are frequently encountered [1] This is not to deny the existence of oxygen intoxication as well as oxygen embolization but serves to draw attention to another potential mechanism that can simulate the response attributed by several discussants yesterday to oxygen intoxication I look forward to hearing more of these embolization phenomenon tomorrow

In Figure 102 is shown the tendency for blood to undergo fibrinolysis after extensive intravascular coagulation has occurred This lytic tendency *appears promptly and is largely dissipated by the* end of the fourth post infusion hour in the experiments we have performed. The bleeding tendency is easily combatted by the administration of fibrinogen The platelet count and the prothrombin activity are severely depressed by extensive intravascular clotting of this type The situation it creates simulates that seen in thrombotic thrombocytopenia in man [1]

It is difficult to assess the presence or absence of *endogenous* anticoagulants under these circumstances if for no other reason than exogenous heparin has already been administered This is a field of much debate in which the established facts are few

Should the hemorrhagic diathesis appear after the shunt or by pass is closed and the exogenous heparin has been neutralized

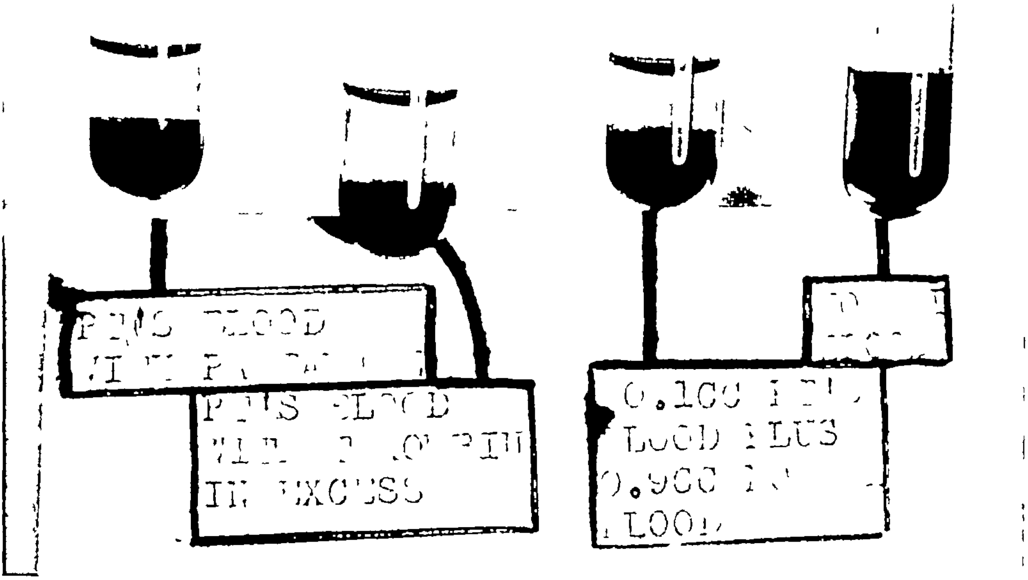


FIG 102 Such extensive fibrinolysin titers developed in the blood of this patient that 0 1 ml of the patient's blood lysed 0 9 ml of normal blood in 30 minutes Note that neither protamine nor thrombin enabled the tubes of blood to clot Lack of coagulation is indicated by sedimentation of red cell mass

by the administration of suitable quantities of protamine, what then? If time permits, the following procedures may prove useful to establish the kinds of therapy that may be indicated

a The determination of the whole blood clotting time by the Lee-White method or by one of its modifications It is most important to save all tubes of clotted blood, placing them in a water bath at 37° C to observe for the occurrence of lysis of the clot Partial or complete lysis may occur in a matter of a few minutes to one hour If the clot remains normal and firm for one hour, lysis is not likely to be the major problem in the hemorrhagic diathesis at the time the sample is drawn, except when all fibrinogen has been digested and no clotting is possible However, any time during the first few hours after closure of the circuit, lysis may develop and create a serious problem in hemostasis Therefore, if bleeding continues and other studies are normal, lysis should be

sought for again before re exploration of the wound for the presence of surgical bleeding due to inadequately ligated vessels unless of course, the latter is obvious Lysis can be easily and rapidly detected and may be associated with hemolysis

b If the blood fails to clot one of two reasons generally will explain this problem when it occurs in the course of the use of extracorporeal circuits or following shortly thereafter Such failures of clots to form are usually due either to the inadequate neutralization of heparin by protamine and indicate that more protamine is required, or to such an extensive lysis of fibrinogen that no coagulable fibrinogen remains To establish the presence of unneutralized heparin a protamine titration of the type described by this laboratory[4] may be useful If the blood coagulates in the tubes containing higher concentrations of protamine the defect is apt to be the presence of unneutralized heparin, although thrombocytopenia and an accelerated rate of fibrinolysin may also coexist Platelet counts to check for thrombocytopenia and the addition of fibrinogen or normal blood to the unclotted sample of the patient s blood, with the incubation of this mixture at 37°C should be carried out to check for the presence of excessive fibrinolytic activity as detailed in the next paragraph

c If the blood sample from the patient fails to coagulate upon the addition of the quantities entailed in the protamine titration, another type of titration is indicated, that of titrating this abnormal blood against normal homologous blood or fibrinogen. A series of 11 chemically clean but *uncoated* serology tubes containing increasing increments of the patient s blood, starting with 0.2 ml with each tube containing progressively 0 2 ml. more of the patient s blood until the final tube contains 2.0 ml of the patient s blood A 20-ml. sample of venous whole blood is then drawn through an *oil-coated* syringe and needle from a normal male human subject and placed in a 50-ml. *oil coated* test tube Using an *oil-coated* graduated 5-ml pipette filled to the 5-ml. gradation 0.2 ml of normal blood is added to the tube containing the 1 8-ml volume of the patient s blood, making a total of 2.0 ml of the mixed blood in 9 of the 11 tubes Thus 0 4 ml 0 6 ml 0 8 ml. etc of the normal blood are added respectively to the tubes containing 1 6 ml 1 4 ml 1 2 ml 1 0 ml 0 8 ml. 0 6 ml.

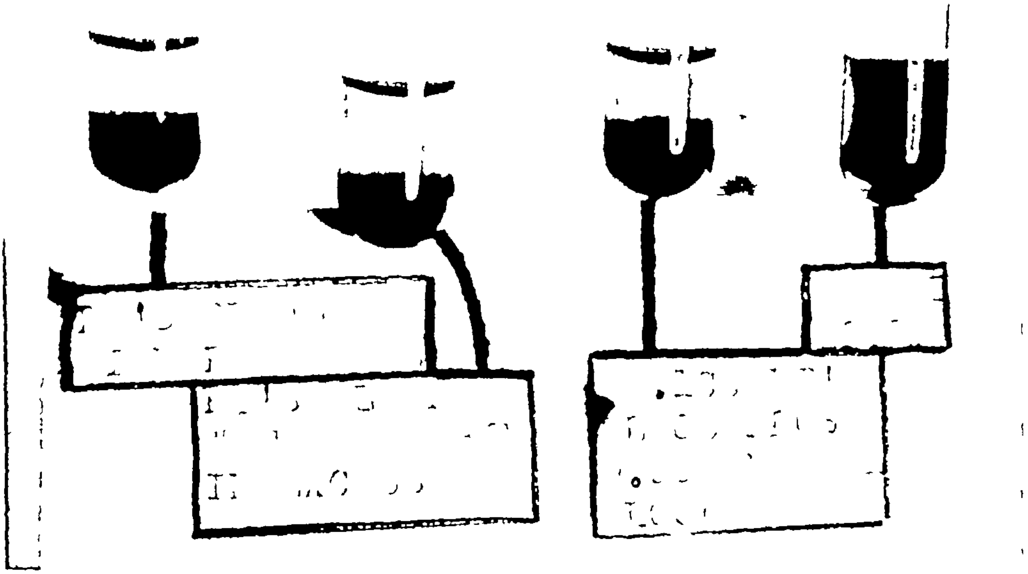


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than from venous blood If severe thrombocytopenia is present, immediate arrangements should be made for the transfusion of platelet concentrates if possible

e Treatment often cannot await the outcome of the laboratory determinations mentioned above However if one prepares for these clotting studies in advance of each operation and with the same care that he does for the use of his extracorporeal circulation at least these studies can be instituted on blood drawn before blind treatment is started There is no objection to blind treatment when it remains within the bounds of good judgment. Basically only two forms of treatment are readily available in that these are the only effective agents which can be stored indefinitely in the facilities of the hospital They are fibrinogen and protamine sulfate Platelets do not retain their full activity when stored by methods which might otherwise seem adaptable to clinical use

Six to 12 grams of fibrinogen should be diluted in 200 ml. of saline and administered intravenously in ten minutes time or less when bleeding is suspected as arising from its depletion. It may be necessary to repeat this dosage or somewhat smaller ones within one to four hours should bleeding recur because of continued lysis of the transfused fibrinogen Usually however the increased fibrinolytic titer diminishes rapidly so that the major concern is the transient replacement of fibrinogen to maintain its near normal concentration until its endogenous production by the subject is capable of supporting this phase of the clotting defect

Fifty mgm of protamine sulfate or about 0 7 mgm per kilo is also administered by vein when bleeding recurs after previous neutralization of heparin by this agent Protamine should not be added to the bottle containing the infusion of fibrinogen as protamine may cause *in vitro* precipitation of fibrinogen We generally administer the 50 mgm or lesser doses of protamine intravenously by the syringe technic over a period of three to five minutes of time This dosage may need to be repeated within thirty minutes to an hour or two later [3]

If we can treat blindly why perform the above laboratory procedures at all? Their chief value is that they may shed some light on the quantities of protamine or fibrinogen that may be needed Moreover these data afford an opportunity to check upon the clot

0.4 ml., 0.2 ml., leaving the 2.0 ml. of the patient's blood, as well as a 2.0 ml. sample of the normal blood, for controls or points of reference. Then, the tube containing the highest percentage in the mixtures of the patient's blood with that of normal blood is the one containing 1.8 ml. with 0.2 ml. of normal blood (90%). The tube containing the lowest percentage of the patient's blood (10%) is the one with 0.2 ml. to which has been added 1.8 ml. of normal blood. Thereby we have a gradient of these mixtures, beginning with 0 per cent and increasing at 10 per cent increments each, until the 100 per cent sample of patient's blood is reached. Each of these tubes is stoppered, placed in a test tube rack, and the rack with all of the tubes is then inverted five times to mix. This simple procedure will detect and titrate crudely the presence of any increase in the fibrinolytic enzymes should they be present in the patient's blood. Samples are shown in Figure 102.

Coagulation will occur in all of the nine tubes containing these mixtures, as well as in the two additional control tubes, if no lytic activity is present in the patient's blood. If lytic activity is present, the end point is taken to be that tube in which no lysis of the clot is evident at the end of the thirty-minute incubation time. Some of those in which clotting occurs will lyse before the end of thirty minutes. One or two tubes containing 10 per cent or 20 per cent less of the patient's blood in their mixtures, may lyse between thirty and sixty minutes or longer. However, the thirty-minute lysis time seems to be practical enough for clinical purposes, considering the urgent need for a prompt answer.

Lysis of the fibrinogen in these blood mixtures may occur before they coagulate when the titer of these enzymes in the patient's blood is extremely high. Then it becomes desirable to repeat the titration at ranges of 1 per cent to 10 per cent to establish an end point. When blood fails to clot in the 10 per cent to 90 per cent range of the usual fibrinolytic concentration, one should suspect the presence of unneutralized heparin; it is for this reason that we have usually set up the protamine titration and the one for detection of fibrinolytic activity at the same time to obtain a prompt answer, if one is obtainable.

d. The platelet count should be determined from a drop of blood obtained from the lobe of the ear or the finger pad rather

ing room generally several hours less storage at 37°C is required How important this may be is not fully known

The effect of these two differences in time and temperature upon the preservation of platelet concentration and presumably also their coagulant effectiveness is not well established It is known however that unless blood is drawn and administered without delay the longer the unit of blood in a plastic bag is allowed to stand at 37°C before administration the more rapid is the deterioration of the platelets it contains Conversely when such blood is promptly refrigerated their rate of disappearance is slower It seems doubtful to me that a final decision as to the merits of one of these methods over the other can be established at this time My discussions with some of those present in this audience disclose that both practices are in use and that the successes and troubles clinically seem to be about equal.

SUMMARY

1 It is pointed out that coagulation is probably a dynamic process which normally functions continuously in a homeostatic fashion This function appears to be essential to the prevention of abnormal bleeding at one end of its homeostatic spectrum and the avoidance of pathologic intravascular coagulation at the other extreme

2 The use of any type of extracorporeal circulation, pump and oxygenator favors coagulation as well as the tendency toward thrombocytopenia The more extensive the extracorporeal circuit and the more mechanical difficulties it imposes the greater is the tendency for coagulation within the circuit, as well as within the circulation of the patient. Similarly the longer the circuit is in use the more extensive these changes will be

3 Many but not all of these changes in coagulation can be prevented by rendering the blood incoagulable with heparin during the period the circuit is open The tendency towards thrombocytopenia is lessened but not abolished by anticoagulation with heparin Fibrinogen concentration tends to remain stable as does the activity of prothrombin if sufficient heparin is administered prior to the use of the extracorporeal circulation and is continued throughout its operation but the platelets drop sharply if inadequate quantities of heparin are used

ting status of the patient within a limited manner for twelve to twenty-four hours after bleeding ceases and, thereby, may forewarn an impending recurrence These methods may also be used to study patients after the extracorporeal circuit is closed and the heparin effect has seemingly been neutralized, in order to evaluate the possibilities for the onset of latent bleeding

There are other changes that occur from extracorporeal circulation of the blood than those affecting coagulation and, indeed, even additional changes in the clotting mechanism which have not been included in this discussion because specific therapy for them does not exist at this time Some degree of hemolysis follows the use of any extracorporeal circuit, pumps and oxygenators, as we heard mentioned yesterday There is good reason to believe that at least two factors contribute to hemolysis under these circumstances, assuming typing and cross-matching of the samples of the donors' bloods disclose no incompatibility and that the blood and equipment are free from bacterial contaminants and pyrogens These factors are the extent to which the characteristics of the system employed favor cellular breakdown and coagulation A second one is the age and conditions under which blood is preserved until it is used A poorly designed pump, oxygenator or extracorporeal circuit increases the extent of hemolysis, the better the design of these components of the circuit, the less will be the hemolysis that does occur The age of the donor's blood affects the fragility of the red cells, as well as that of the platelets they contain Age increases exponentially the rate of hemolysis under standard conditions in relation to temperature, the sooner a unit of blood is refrigerated (2°C to 6°C), the longer it will maintain its near-normal tolerance for the insults which result in hemolysis This fact creates a dilemma which is not easily resolved in the use of blood for extracorporeal circulation If one does not draw the blood from his donors until the morning of surgery and thereby avoids refrigeration, he generally will allow his samples of blood to remain longer at 37°C than when blood is drawn and refrigerated the night before There are unavoidable delays encountered in scheduling donors for phlebotomy early in the morning When the donors are bled late in the evening of the day before surgery and all units are immediately placed under refrigeration until two hours prior to warming for immediate use in the operat-

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4. The neutralization of intravenous heparin by the administration of a milligram for milligram dose of intravenously injected protamine sulfate is sufficient, except when thrombocytopenia develops Then 1 25 to 1 50 mg of protamine sulfate may be necessary to overcome each milligram of heparin recently administered, due to the capacity of platelets to neutralize heparin Thus, the more extensive the thrombocytopenia, the greater is the quantity of protamine required to bind heparin, for it must neutralize that portion of heparin which was previously held inactive by the circulating platelets prior to their depletion However, the dosage of protamine should not exceed 3 0 mg per kilo of body weight unless massive dosages of heparin have been used As protamine is destroyed *in vivo* more rapidly than heparin, a second dosage of protamine equal to about half the initial one may be required one to three hours later to prevent recurrence of bleeding

5 The accelerated rate of fibrin and fibrinogen destruction may be encountered in the use of an extracorporeal circuit Its stimulus is thought to be inadequate heparinization, permitting the formation of minute intravascular clots throughout the capillary circulatory bed, including the lung, liver, kidney and brain as demonstrated experimentally This results in the partial or total depletion of fibrinogen, prothrombin, and platelets, and an increase in fibrinolytic titers which may reach sufficient levels to destroy for several hours while new fibrinogen is being formed Treatment of this condition is the transfusion of 6 to 12 grams of intravenously administered fibrinogen, the futility of blood transfusions in this respect, other than to sustain blood volume, is discussed

6 Simple laboratory procedures useful for the detection of inadequate neutralization of heparin, the depletion of fibrinogen and the existence of excessive titers of fibrinolysin are described Their routine use after operation is encouraged as an aid for the prescription of treatment, as well as indicators of the potentials of impending hemorrhage in patients in whom extracorporeal circulation has been employed

7 The choice of time most suitable to the bleeding of donors in relation to that of the operation is discussed The time and temperature factors affect the fragility of the donor's red cells, as well as the intact survival of his platelets

ADDENDUM

Because many have inquired about the disposition of units of heparinized blood should the patient's condition during surgery prove to be inoperable the following procedures may be helpful in the salvage of these units of blood provided each unit is proven to be bacteriologically sterile or that it can be administered under appropriate circumstances within 12 hours to another patient As soon as the fact is established that the transfusions will not be used in the by pass procedure these units should be refrigerated immediately to retard bacterial growth should contamination have occurred The duration of incubation of each of these units at temperatures above 20°C should be noted and recorded If the storage at "room temperature" or higher (35° to 41 C) exceeds three hours none of these units should be reused without first determining that each is bacteriologically sterile by culture methods If the storage time at these elevated temperatures has been less than three hours and the units thereafter refrigerated promptly it is *usually* safe to administer them to other patients within the next twelve hours If they are not called for within this period, each should be cultured and the data known prior to their release

Although these units of blood are heparinized and contain 5% dextrose it is generally good practice to add the usual quantity of sodium citrate anticoagulant solution employed for the collection of blood for ordinary transfusion purposes If glucose is not used originally then ACD solution rather than citrate should be added This is done by the insertion of a needle through the closed container after cleansing the surface about the proposed point of entrance with an antiseptic solution preferably tincture of iodine or by flaming if practical Attached by "Luer lok" to the 20-22 gauge needle is a 50-ml syringe containing 50 ml. of a 2% sodium citrate solution After this solution is introduced and with the needle and syringe left in place gentle shaking of the unit is done to obtain mixing Then 10 ml of the blood is aspirated into the same syringe and the needle withdrawn from the container The sample of aspirated blood is cultured The expiration date should be considerably less than 21 days preferably less than 7 days

No attempt should be made to neutralize the heparin *in vitro* by the direct administration of protamine sulfate to the unit of

blood. Should the patient receive these transfusions during the course of an operative procedure or for replacement of blood loss from any nonoperative bleeding state, then milligram-for-milligram protamine neutralization of heparin may be administered through another intravenous set during the course of transfusion with these units of blood However, unless these transfusions are given rapidly and in large numbers (4 or more), protamine neutralization is seldom indicated

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PROBLEMS IN COAGULATION*

By

HERBERT A PERKINS, JOHN J OSBORN, *and* FRANK GERBODE

THE EFFECT of pump-oxygenators on the blood has commanded high interest from the first, inasmuch as this is the part of the patient that comes into direct contact with the artificial external circulation The use of clean non wettable surfaces and the avoidance of unnecessary turbulence and trauma to the blood has made it possible to prevent clotting in the machine with predictable and reasonably low levels of heparin However a postoperative hemorrhagic syndrome was a major obstacle to the successful use of pump-oxygenators by early workers in this field and apparently is still a problem to many of the newcomers

We have been studying the effects of extracorporeal circulation on the blood intensively for more than two years A number of different types of both bubble and film oxygenators have been used. Although abnormal postoperative bleeding was seen in only a few instances at the beginning of this period we have been able to demonstrate several mechanisms by which a hemorrhagic diathesis may occur

It is natural to assume that heparin is responsible for the hemorrhagic tendency in view of the obvious fact that oozing from an operative site may occur in a heparinized patient because clotting is prevented in vessels which have not been adequately closed by suture However the primary mechanism by which bleeding from small vessels is arrested is the formation of a platelet plug a process which is less likely to be inhibited by heparin and it is remarkable how dry a field adequate hemostatasis can secure in a fully heparinized patient Moreover after the by pass

* Supported by a United States Public Health Service Grant.

is over, the clot-inhibiting effect of heparin should be completely eliminated by a proper dose of protamine We are not afraid of too much heparin, there is no evidence that a large dose of heparin will result in any more bleeding than an adequate amount Too small a dose will definitely cause trouble There is a marked difference in the requirement for heparin, depending on the individual patient and the surfaces to which blood is exposed We have seen unexpected clotting in one case in which a by-pass around an aortic aneurysm was performed through a pump and a relatively short length of polyvinyl tubing for forty-five minutes The patient had been given 1 mgm of heparin per kilogram, a dose usually considered adequate for this procedure When the by-pass was taken apart the lumen of the tubing was found to be markedly narrowed by a thick fibrin deposit on the wall At present we are using a heparin dose of 3 mgm per kilogram for all of our by-passes

Despite what has just been said about not being afraid of excess heparin, it is still wise to neutralize the remaining heparin at the conclusion of the by-pass It is much easier to stop the oozing of blood from incisions in high pressure arteries and the heart if the clotting time is restored to normal There is an advantage, however, to delaying administration of protamine for a short while, because the increased oozing that occurs in the presence of heparin forces the surgeons to achieve more meticulous hemostasis

The most commonly used method of calculating the dose of protamine seems to be to give the same dose as had been employed for the heparin, and if the clotting time is still prolonged, to give a little more We have had a considerable amount of experience with a simplified protamine titration test which calculates for us the minimum required dose of protamine [1] Table I shows that when protamine was administered in accordance with this technique, subsequent titrations almost never showed a need for additional protamine, and then only very minimal amounts It should be made clear that in calculating the dose of protamine required it is necessary to assume that the protamine will be diffused in a volume of 100 ml per kilogram of body weight This is higher than the circulating blood volume and suggests

TABLE I

PROTAMINE TITRATIONS

Experiments are listed in the order performed During the last four by-passes the patient was given a heparin dose of 3 mgm per kilo All prior operations were with a dose of 2.5 mgm per kilo

PROTAMINE TITRATIONS

REQUIREMENT – MCG/ML BLOOD

	AFTER BY PASS	5 MINS	15 MINS	30 MINS	45 MINS	1 HOUR	2 HOURS	3 HOURS
1 DOGS	20			5		0		
	10	0				0		
	15							0
	10				0			
	25		0					
2 HUMANS	20		0					
	15		0		0			
	20							
	30							
	30						0	
	25					0		
	25					0		
	25							0
	25					0		
	20				0			
	30						0	
	30					0		
	25						0	
	35					5	0	

that heparin and protamine diffuse to some extent into extra vascular spaces

We give protamine in a single injection administered over a period of three to ten minutes Our requirement for protamine as measured by the titration technique appears to have steadily increased during the past two years On several occasions during the early part of this period we caused abnormal prolongation of the clotting time of a dog by protamine excess while giving the same dose as had been used for heparin More recently we find that our requirement is approximately 1.2 mgm of protamine for each mgm of heparin administered to the patient We explain our increasing requirement for protamine by assuming that improvement in the surfaces of our external circulation and better avoidance of trauma results in less activation of clotting factors

and thus less neutralization of heparin. This remains to be proved.

We have been puzzled by the reports of heparin rebound. We have never seen it. Table I reveals no instance of reappearance of heparin after it had been neutralized. The data are reinforced by many more operations not included in the table. We have attempted to see if heparin rebound could be produced by using the maximally safe as well as the minimum necessary doses of protamine. It made no difference. We have never found the clotting time prolonged again after it had once been returned to normal. We are aware of no possible way to explain the phenomenon of heparin rebound, if it does exist.

From what has just been said, it is obvious that excessive postoperative bleeding could occur with either too little or too much protamine. There is a wide range of safety between these two extremes, however, and with the availability of protamine titration techniques there is no excuse for bleeding for these reasons. The protamine titration has the added advantage that it can be used to determine the need for additional heparin during a prolonged by-pass. It can also indicate if the clotting time is prolonged for reasons unrelated to heparin or protamine.

The next question is whether alterations in the patient's blood coagulation factors can explain abnormal bleeding after the by-pass. Several years ago Osborn[2] showed that some of the extracorporeal circulations then employed experimentally would remove fibrinogen from blood to a degree that might result in hemorrhage. Clot lysis also was noted. The exact mechanism involved is not clear. It may have been due to activation of coagulation, particularly if inadequate amounts of heparin were present, or to direct denaturation by trauma.

Our present series of investigations, however, with a number of different pump-oxygenators on both dogs and humans, shows a negligible loss of fibrinogen (Figure 103). Similar results have been reported by others. It seems apparent that with present techniques loss of fibrinogen due to the machines need be given little consideration. Nevertheless, there is still the possibility of activation of the fibrinolytic system which occurs occasionally and unpredictably with certain types of major surgery, possibly due to epinephrine secretion. We have had two experiences which,

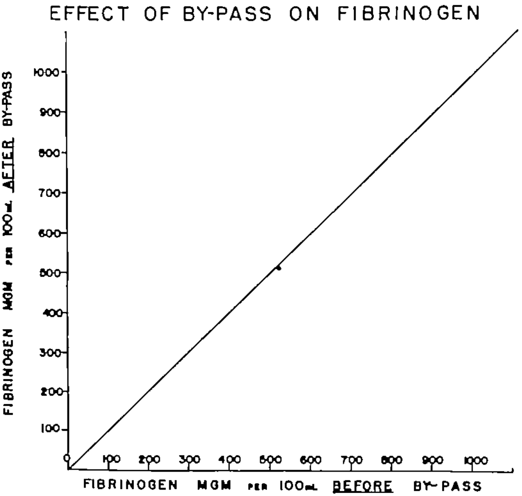


FIG 103 Effect of By pass on Fibrinogen Each point on the chart represents the results obtained during a single by-pass, its horizontal displacement representing the level before by pass its vertical displacement the level after by pass The 45 angle line is the line on which all points would fall if there were no change in the fibrinogen level during by pass

though harmless have made us keep this possibility in mind The first was when a blood sample taken for cross matching purposes on one of our patients was found liquid after 8 hours in the refrigerator The child had had an extreme emotional reaction to the venepuncture A subsequent sample clotted normally The second episode occurred when a protamine titration done at the beginning of a by pass failed to show a clot. Repeated clotting tests at later intervals on that day were normal. The fibrinogen levels rose gradually to normal from a low of 96 mgm% before the by pass (Table II) This patient showed no unusual bleeding In

both these cases, then, the fibrinolysis was transitory and asymptomatic Clinically significant fibrinolysis has not been seen, but remains a possibility

Plasma coagulation factors other than fibrinogen are more difficult to assay None of the available techniques can detect small variations with accuracy It is not yet clear how much these tests are altered in a patient who has been heparinized and then given an excess of protamine We have not done a sufficient number of these tests to feel dogmatic, but scattered tests of the prothrombin time and prothrombin consumption on patients who have received the minimum necessary dose of protamine have revealed results in a completely safe range Personal communications from several other sources confirm these results, but we plan to investigate this aspect of the problem more thoroughly

TABLE II

FIBRINOGEN LEVELS IN PATIENT WITH TEMPORARY DEFECT

Time	*Fibrinogen mgm per 100 ml*
12 45 p m (start of by-pass)	96
1 15 p m (end of by-pass)	171
2 25 p m	252
4 05 p m	316

Changes in the blood platelet count during by-pass have been extensively studied and are being reported in detail elsewhere [3] There is a considerable variation from case to case due to the multiplicity of factors affecting the platelet count However, the general trend is for a marked drop in the platelet count, averaging approximately 50% Since platelets are notoriously sensitive to trauma and to various surfaces we had hoped that they might provide a sensitive index of the relative degree of harmfulness of different pump-oxygenators We were somewhat disappointed, however, to find no difference in the degree of platelet change between bubble and film oxygenators As we examine our figures in regard to platelet loss over the last 2 years we find that in general we are losing just as many platelets as we did 2 years ago However, in the early months of this investigation several experiments did occur in which the platelet count dropped below 60,000 per cu mm , in other words, to levels that could result in

a hemorrhagic syndrome These low platelet levels were associated with postoperative oozing from the wound and bleeding into the gastrointestinal tract Such low counts at the end of the by pass have not been seen in the past 2 years though it is not rare for the platelet count to drop to 100 000 per cu mm It usually returns quickly to safer levels after the extracorporeal circulation has been discontinued

The extremely low platelet counts of these few early experiments were due we believe to pyrogens or other foreign matter on the surface of our pump-oxygenator We were not then insisting upon the meticulous degree of cleanliness that is necessary for these procedures The effect of pyrogens was brought home to us by a series of experiments in which a very severe drop in the white blood cell and platelet count occurred before by pass The fault was traced to a dirty blood pressure recording catheter

As stated above our extracorporeal circulations have not depressed the platelet counts to levels usually associated with bleeding in the last two years nonetheless we still have not been able to conclude that platelets can be ignored as a possible cause of a hemorrhagic tendency Close inspection of our figures shows that in a number of cases the counts remained below control levels for several days suggesting the possibility that the body s reserve of platelets may have been depleted This is borne out by one case in which a postoperative hemorrhage required an additional transfusion of 4 000 ml of blood The platelet count, which had risen to normal with some delay after the by pass fell to very low levels for a number of days (Table III) Moreover frequent checks of the platelet counts during by pass indicate that although the greatest loss occurs in the first 5 minutes the fall continues at a much slower rate throughout the procedure These facts suggest that thrombocytopenia might become of clinical importance following by passes of much longer duration The one long by pass we have performed (which lasted 4 hours) still left 90 000 platelets in the blood at the end of that time These may well have been largely donor platelets with a very short survival time but the patient expired at that point preventing further follow up

In summary we believe that a postoperative bleeding syndrome can be produced by at least three different mechanisms (1) insuf

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DISCUSSIONS ON BLOOD CHANGES IN EXTRACORPOREAL CIRCULATION

DR IVAN W BROWN JR Durham We have been interested for some time in the effects of extracorporeal circulation on the cellular elements of the blood I would like to confine my remarks to the effects on red blood cells that we have observed in some of our studies

We have studied the effects of the DeWall bubble oxygenator and

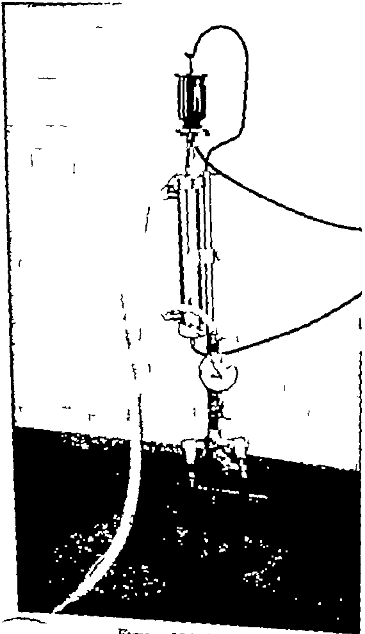


FIGURE 104 (Brown)

TABLE III

PLATELET CHANGES WITH BYPASS PLUS MULTIPLE TRANSFUSIONS

Time	Platelet Count
Before surgery	135,000
Before by-pass	173,000
End of by-pass	93,000
1 hr after by-pass	88,000
3 hrs	225,000
8 units of blood given	
1 day	63,000
2 days	48,000
3 days	55,000
5 days	140,000
7 days	238,000

ficient or excessive protamine, (ii) thrombocytopenia (especially from inadequately cleaned equipment), or (iii) fibrinolysis related to the surgical procedure itself The corollary of this is that if a patient continues to lose an abnormal and dangerous amount of blood from the chest drains, but has a normal clotting time with a good firm clot and has an adequate platelet count, he should be re-explored with the expectation of finding a bleeding vessel which needs ligation

REFERENCES

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2 Osborn, John Jay, MacKenzie, Ronald, Shaw, Anthony, Perkins, Herbert, Hurt, Raymond and Gerbode, Frank Cause and prevention of hemorrhage following Extracorporeal Circulation In *Surgical Forum* VI, 1955, Philadelphia, Saunders, 1956, pp 97-100

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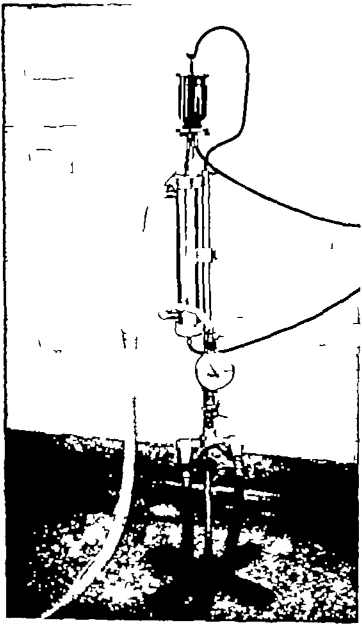


FIGURE 104 (Brown)

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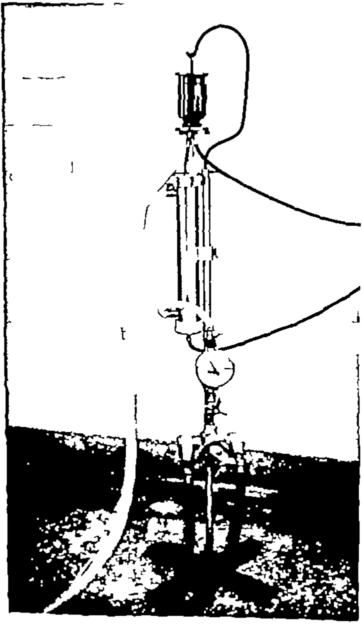


FIGURE 104 (Brown)

our own plastic bag oxygenator on *in vivo* red cell survival In addition, as Dr Sealy indicated this morning, our patients are operated upon with a combination of hypothermia and extracorporeal circulation Figure 104 illustrates our blood heat exchanger with which we are conducting studies at the present time This simple device is inserted in the inflow line to the patient The blood leaving the top of the exchanger stays within 0 3°F of the circulating heat exchanger fluid The temperature of the latter can be regulated precisely up or down

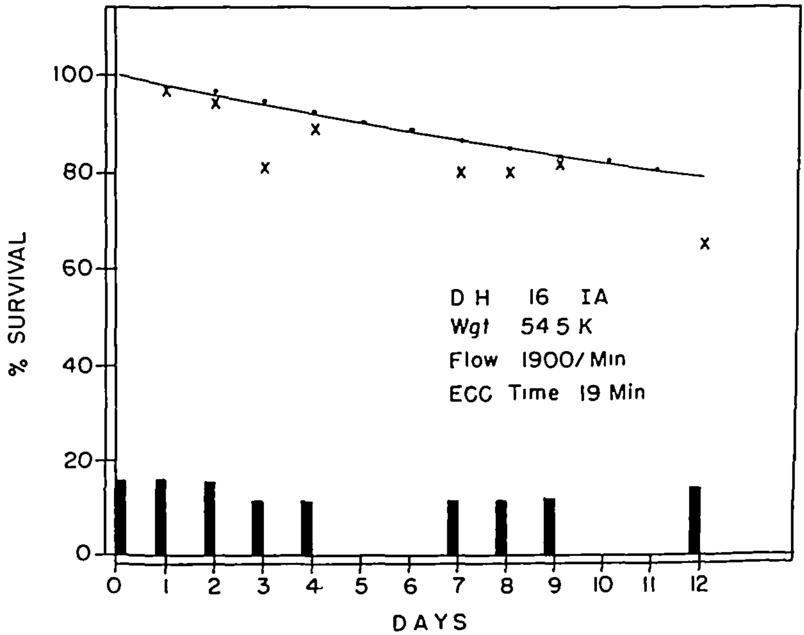


Figure 105 (Brown)

permitting absolute control of the blood inflow temperature and thus also the patient's temperature

The data in Figure 105 are representative of a large number of *in vivo* red cell survival studies carried out during the first twelve postoperative days on patients following open cardiotomy under extracorporeal circulation and hypothermia The solid line is the normal expected red call decay curve with time The X's represent survival as determined by Cr^{51} tagging Note that these latter points fall close to the slope of the normal survival curve

This has been the case in all our studies for the first ten to fourteen days postoperatively whether the DeWall bubble oxygenator or our own plastic bag filming oxygenator was used The survival was normal during this interval whether we tagged the patient's own red cells, the donor red cells or both

However when we followed the donor red cell survival over longer periods, we found that after an interval of twelve to twenty days of normal survival, these cells would occasionally disappear or rapidly drop along a sigmoid slope Figure 106 represents such drops of donor red cells in normal compatible recipients after recirculating through the pump oxygenator and patient s circulation (X — 24 min) (— 2 1/2 hrs) At first it was difficult to account for these sudden late drops in

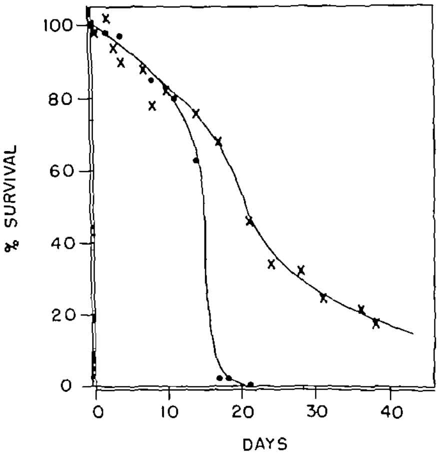


FIGURE 106 (Brown)

red cells but we have recently been able to show that they are due to antibodies provoked in these recipients by the lesser antigenic blood groups Additional survival studies made with tagged red cells which had merely recirculated through the pump oxygenator for varying intervals then divided into aliquots and transfused back into the original donor and a number of normal compatible recipients also show this same phenomenon but never in the original donor The number of compatible recipients developing antibodies after an interval with

rapid disappearance of the remaining cells is a significantly high percentage and raises the question as to whether the pump oxygenator circuit might in some way render the lesser blood group antigens of these cells more antigenic than found in ordinary transfused red cells

DR CHARLES K KIRBY, Philadelphia Dr. Harold Wurzel and his associates of our coagulation group, and Dr Robert Norris, head of our Blood Bank have thought that it is relatively safe to draw the heparinized blood the night before the operation They found that the platelet count might fall to 100,000 or even 60,000 when checked preoperatively the following morning. At present, this thrombocytopenia is thought to be caused by heparin Since these platelet levels have

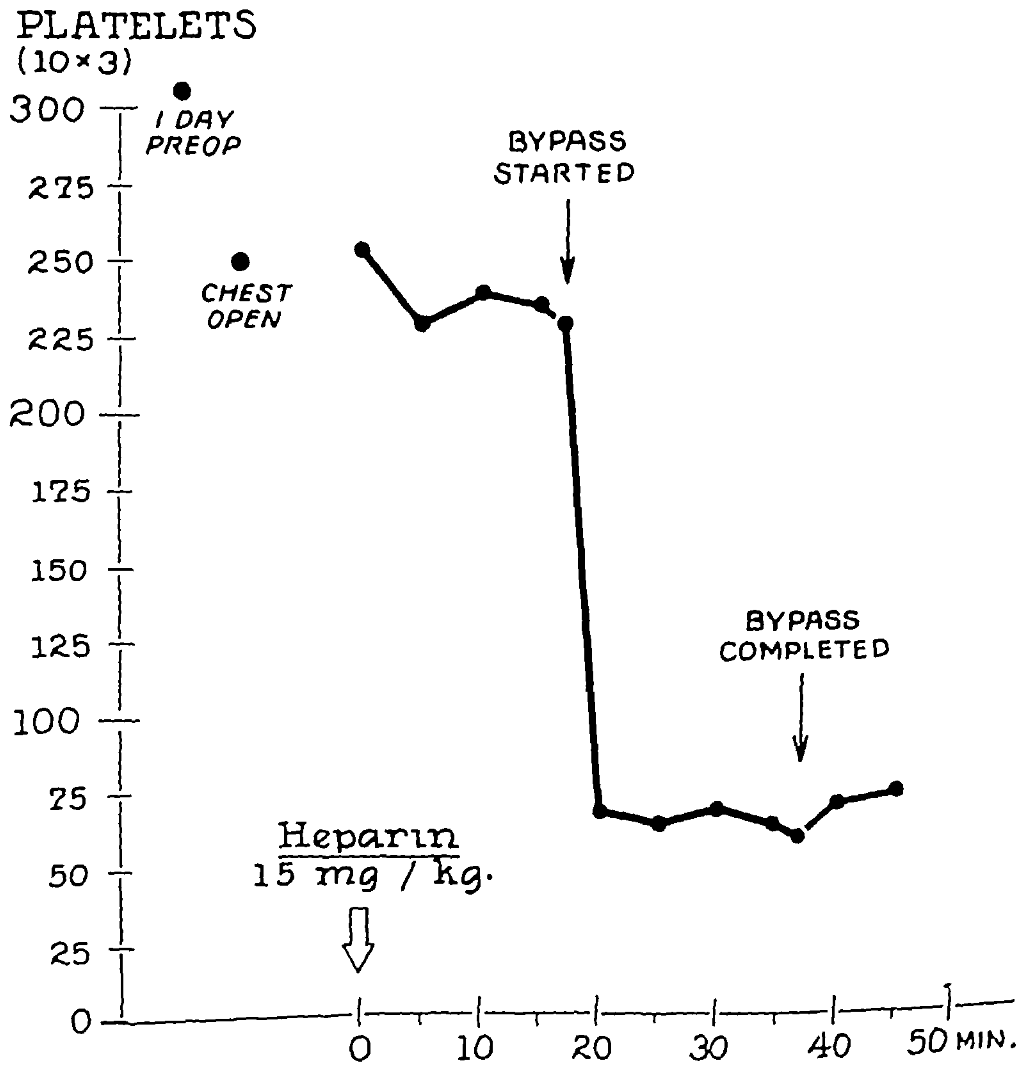


FIGURE 107 (Kirby)

been in the range associated at times with clinical bleeding, we have all been concerned about the possibility of an increased hemorrhagic tendency

First slide, please, Figure 107

This is a composite chart showing the platelet response of three patients Heparinization prior to insertion of the caval and arterial cannulae did not alter the patient s platelet count very much. You will

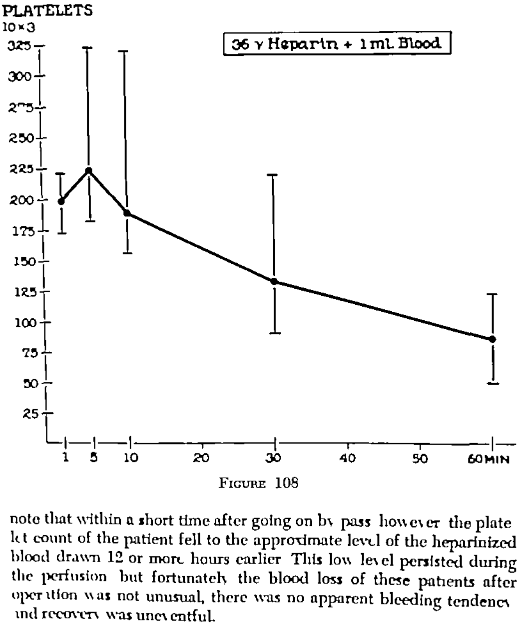


FIGURE 108

note that within a short time after going on by pass however the platelet count of the patient fell to the approximate level of the heparinized blood drawn 12 or more hours earlier This low level persisted during the perfusion but fortunately the blood loss of these patients after operation was not unusual, there was no apparent bleeding tendency and recovery was uneventful.

Second slide please Figure 108

This is an *in vitro* study of the effect of the usual heparin dosage (18 mgm per 500 cc blood) in six donors as related to time The mean of the platelet counts and the range are shown In these instances, the decrease in platelets was rather striking within thirty minutes and within an hour had fallen well down towards the levels which were noted after 12 hours, as I previously mentioned The mechanism and the possible clinical significance of this thrombocytopenia are being carefully studied

DR. ANDREW G MORROW, National Heart Institute I would like to know what evidence we have about the advisability of bleeding our donors the night before operation, or whether it is necessary to bleed them just before perfusion is carried out

DR LLOYD NYHUS, Seattle During the past twenty-four hours we have heard considerable reference to sudden death following the use of extracorporeal circulation Not all of the etiologic mechanisms for these tragedies are known Various symptoms and signs have been presented here as a part of the syndrome—cyanosis, mottling of the skin, hypotension and coma Oxygen intoxication and various other mechanisms have been discussed as being the causative mechanism

I should like to suggest a rather different approach which may or may not bear fruit During a series of experiments, utilizing a pump oxygenator for perfusion of isolated organs, primarily liver, we have been struck by the response of the liver to this perfusion Severe edema of the liver has resulted from this perfusion, the etiology of which has been difficult to explain It has been suggested that the breakdown of infused white blood cells may release an excessive amount of histamine into the system Many of the responses presented as a part of the sudden death syndrome could be envisioned as part of a general histamine-like response

Another chemical which must be considered is 5-hydroxy-trypamine or Serotonin Platelets are known to be rich in this material and the breakdown of donor and of recipient platelets by the pump-oxygenator system, with release of excessive quantities of Serotonin could present a clinical picture of skin mottling, cyanosis, etc

DR EDWARD S HYMAN, New Orleans A couple of years ago in playing with oxygenators we noted a relationship between foaming and clotting that appeared with long runs or when too little heparin was used This can be reproduced in test tubes In these slides (not repro

duced—Ed.) there are two test tubes containing Silicone Antifoam A the one on the right contains heparin and the one on the left does not Timing started with the venipuncture An oxygen stream flows through identical No 20 spinal needles into the tube containing hep arinized blood and another is bubbled through unheparinized blood You will note in forty seven seconds that there is more foam in the tube of blood containing no heparin In sixty one seconds the differ ence is greater at one minute forty six seconds even greater and at two minutes forty six seconds the left tube is about to overflow with the non heparinized blood In three minutes and nine seconds the foam in this tube starts to overflow and at five minutes there is considerable over flow A third tube of this same blood clotted at five minutes when not agitated and non heparinized. Excessive foaming in the course of the use of a pump oxygenator suggests that anticoagulation and heparin may be inadequate and that clotting or defibrination is taking place

(NOTE The action of heparin on surface tension is well known and the observations by Dr Hyman that excessive foaming should forewarn of impending coagulation is a good one Some of the commonly used detergents have an anticoagulant action. —Ed.)

DR. HENRY SWAN II Denver Colo We have been using a fixed screen oxygenation system with the DeBakey pump My colleague has been testing the clotting system by means of a clotting machine which describes a vascular clotting mechanism It is a coagulogram It is based on the principle which Dr Simeone worked out and was originally described by Dr Cannon. Two fingers constantly open and close with a drop of blood between them The response will depend on the formation of the clot. This is photographed electronically

At the top of Figure 109 is a normal coagulogram Here is the clotting time for the clot formation and shows the shape of the curve with the normal formation of the clot The line remains straight for almost a five hour period After anesthesia the clot is normal and the clotting time is essentially normal, but the two lines approach each other at this end, showing very slight fibrination as time goes by The englobulin lysis time is shown where the arrows are In line C there is no clotting at all This is the response of the heparinized patient No clot formation is present. Following perfusion one sees an increase in the time when no clot is formed There is increased anti-coagulant The clot is formed but the two lines approach each other and so there is a low level of fibrinolysin Six or eight hours later the normal response has been restored In line D of Figure 110 is what we have found with

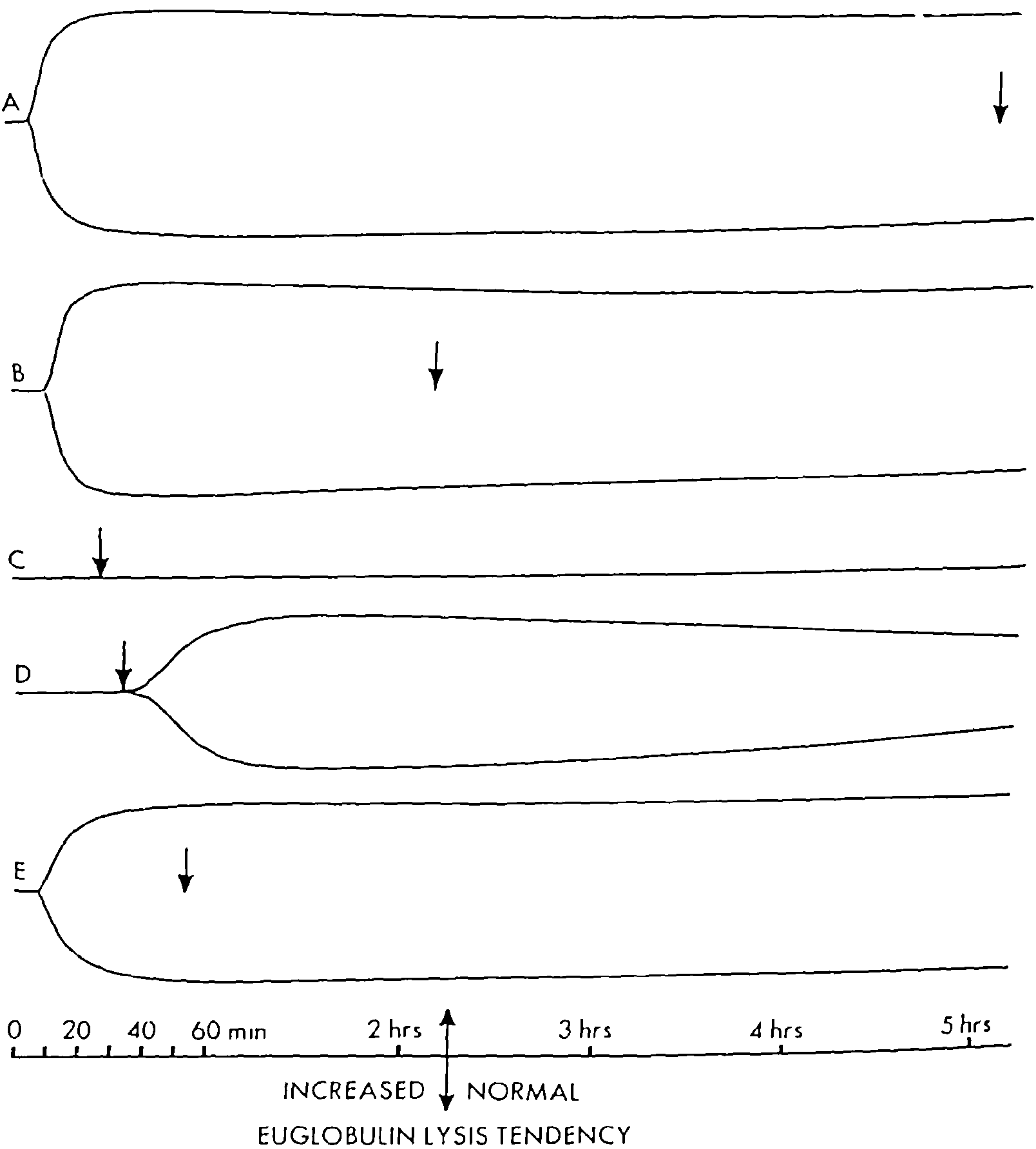


FIGURE 109 (H Swan)

varying degrees of mechanisms in various types of oxygenators and pumps It shows there is an increased amount of anticoagulant and an increased amount of fibrinization This top line D in Figure 110 is the immediate post-pump situation in which you see not too much prolongation of the anticoagulant This is a most extreme picture we have seen of fibrinolysis under any circumstances at all In line E the patient looks as if he had been heparinized, more protamine was given and finally about four hours later in line C we see a most abnormal disturbance This patient had a severe bleeding tendency This can

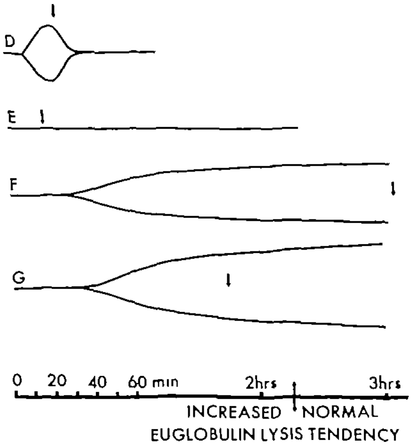


FIGURE 110 (H Swan)

occur without clinical evidence of bleeding We have not had a patient who has not shown disturbance of the clotting mechanism

DR DENTON A COOLEY Houston Dr Morrow and Dr Hanlon have raised a practical question which I believe important since the procurement of blood is the main bottleneck to our production line Because of the difficulty encountered in trying to draw blood on the day of operation during the past four months we have procured blood twelve to twenty four hours in advance of operation Dr Jack Abbott performed studies on this blood which indicate that this is a practical and relatively safe method of providing blood for the pump At the end of twenty four hours platelet counts were 75 000 to 150 000 in refrigerated heparinized blood A less significant reduction in leukocyte count occurred in the same period No important change in the fragility of the red cells was detected during the first 24 hours and their fragility after 72 hours storage was not greatly increased

One must consider that the pH in stored blood may fall to low levels particularly if the blood is not refrigerated continuously We rewarm the blood immediately before using it in the pump oxygenator to avoid this problem If we leave the blood after rewarming for an hour or two at room temperature before starting the perfusion, we will find that the pH may be as low as 6 9 or 6 5

Another problem to consider is the possibility of bacterial contamination and growth of these bacterial agents in the blood In one of our patients we used a pint of rewarmed blood, drawn 12 hours previously, which was accidentally heavily contaminated with staphylococcus It was incubated for two hours prior to transfusion The patient developed a serious bacteremia which was finally controlled, and she recovered after a stormy course This may be another reason for not rewarming the blood too far in advance of operation

Since we have been drawing blood twelve to eighteen hours before operation, we have noted anemia appearing several days after, usually the fourth or fifth day after perfusion This has not been accompanied by an increase in serum bilirubin to our knowledge, but the anemia is more striking than that seen when freshly drawn blood is used in the pump oxygenator In spite of the disadvantages which I have presented for collecting blood on the day before operation, we believe the advantages and the convenience of this method justify continuation of this procedure

DR SIGMUND WESOLOWSKI, Brooklyn I would like to make a few comments on the effect of pumps on the blood The effect is essentially one of trauma We have observed in dogs, which had been subjected to total cardiopulmonary by-pass, progressive changes in the organized elements of the blood during the week following by-pass The platelet level reached a minimum of 30 to 50% reduction in the first three to four postoperative days and returned to normal by the end of the first week The leukocyte count increased in the absence of infection and remained elevated for ten days We noted an elevation of free plasma hemoglobin that reached a maximum twelve hours after the cessation of by-pass and a persistently elevated level during the first three to five postoperative days A single injection of hemoglobin is cleared from dog's plasma within a twelve-hour period so that these findings imply continued intravascular hemolysis during the first three to five postoperative days The finding of progressive drop in the hematocrit value in the face of continued normal blood volume helps to confirm this view I do not think, therefore, that the finding of

post perfusion anemia during the first postoperative week need necessarily prove that the collection of perfusing blood the evening before operation constitutes improper blood collection as suggested by Dr Cooley

I also feel that someone during this conference should point out that the extracorporeal blood pumping circuit is only second best to the one in the body It is a traumatic thing just as surely as an incision into the abdominal wall is traumatic. This also implies of course that we have the responsibility to take all reasonable measures to minimize this trauma

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THE EFFECTS OF EXTRACORPOREAL CIRCULATION ON THE BRAIN

By

ROBERT T. PATRICK, M.D., JOHN W. KIRKLIN, M.D., *and* RICHARD A. THEYE, M.D.

PROPERLY conducted open intracardiac surgery utilizing extracorporeal circulation has no discernible adverse effect on the brain. Evidence will be offered in support of this belief.

Consideration of the effects of extracorporeal circulation on the brain may be properly begun with a review of the features of such perfusion which conceivably could influence the brain. These features would include the volume of blood flowing to the brain and the constituents or physicochemical properties of that blood as it reaches the brain.

VOLUME OF BLOOD

The volume of blood normally flowing to the brain, that is the cerebral blood flow, is about 50 cc. per 100 gm. of brain tissue per minute,[1] as commonly expressed, or approximately 15 per cent of the total blood flow. Reduction of cerebral blood flow by as much as 35 per cent will cause symptoms in conscious human beings.[2] The level to which cerebral blood flow can be reduced without loss of viability of the cells of the brain is unknown.

Blood Pressure.—It is well known that cerebral blood flow is determined largely by the systemic arterial blood pressure and cerebrovascular resistance. Arterial blood pressure in intact man and in man during extracorporeal circulation is a function of total blood flow and total peripheral resistance. Total blood flow to the patient is a controllable feature of extracorporeal circulation. If

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

total blood flow is controlled and unvarying during perfusion blood pressure depends on the state of the peripheral vascular bed. Under conditions of perfusion in which total blood flow is less than normal, arterial blood pressure can be maintained at or near normal only by compensatory vasoconstriction or by over filling the vascular bed Under the latter circumstance the ad vantage of normal mean blood pressure is partially overcome by virtue of the fact that venous pressure increases The effective driving force would be that of the gradient between arterial and venous pressures During perfusion then it would seem desirable to provide to the patient a total blood flow near normal cardiac output while blood volume remains normal

Another factor of extracorporeal circulation having potential influence on cerebral blood flow is the level of venous pressure in the veins draining the brain Laminar flow of fluid through a tube is proportional to the fourth power of the diameter of the tube and inversely proportional to the length of the tube Insertion of a cannula of excessive length into the superior vena cava which compromises the lumen to even a small degree can cause marked elevation of pressure in the superior vena cava cephalad to the cannula with resulting decrease in the pressure gradient across the brain In addition corresponding increase in capillary pressure should it exceed osmotic pressure of the blood will result in cerebral edema

Cerebrovascular Resistance —The second factor influencing cerebral blood flow is the cerebrovascular resistance Given an unvarying total blood flow and an unvarying arterial blood pressure cerebral blood flow will vary inversely with cerebrovascular resistance The cerebrovascular bed does not react strongly to influences usually associated with reactivity in other vascular beds There are however a few exceptions[1] to this statement The cerebrovascular bed is highly sensitive to variations in oxygen and carbon dioxide tension This is particularly true in the case of a decrease in oxygen tension or an increase in carbon dioxide tension Both of these influences markedly decrease cerebrovascular resistance thereby increasing the proportion of the total blood flow diverted to the brain Conversely an increase in oxygen tension or a decrease in carbon dioxide tension will cause

a rise in cerebrovascular resistance with a resulting reduction in cerebral blood flow The effects of variations in oxygen and carbon dioxide tension tending to decrease flow are less pronounced than those tending to increase flow An absolute requirement for normal cerebral blood flow in the presence of less than normal total blood flow and systemic blood pressure is a corresponding reduction in cerebrovascular resistance The factor which at present is known to have the most profound influence on cerebrovascular resistance is the tension of carbon dioxide It seems reasonable then that the tension of carbon dioxide in the blood returned to the patient by perfusion should not be materially less than that normally found in arterial blood

Finally, a linear increase in cerebrovascular resistance has been demonstrated with reduction in body temperature, a potential effect of extracorporeal circulation [3]

Time and Deficient Flow.—The element of time deserves some thought in a consideration of the relationship of cerebral blood flow and brain damage The brain can survive perhaps three or four minutes without blood flow Could one not assume that this time would be extended, should some fraction of the normal quantity of blood be flowing? Would it not seem logical then to assume that for a given deficient cerebral blood flow there would be a critical point of time beyond which brain cells would not remain viable?

QUALITY OF BLOOD

Having discussed the quantity of blood reaching the brain, our attention may properly be turned to the quality of that blood

The oxygen tension of arterial blood of man breathing room air is about 100 mm of mercury It is generally accepted that the oxygen tension of blood pumped to the patient should not be less The tension acceptable as maximum is open to some question Man breathing 100 per cent oxygen at two or three times atmospheric pressure may suffer symptoms referable to the central nervous system, or so-called oxygen toxicity [4] At what oxygen tension such toxicity might be manifest under the rather unusual circumstances of whole body perfusion is unknown Exposure of blood to a high concentration of oxygen in the oxygenator at or

near room temperature may result in a tension of oxygen greater than atmospheric pressure in the warmer vascular system of the patient, by virtue of the increased solubility of oxygen in blood at lower temperatures

The carbon dioxide tension of tissue is somewhat more than 40 mm. of mercury It is necessary then that the carbon dioxide tension of arterial blood be at 40 mm of mercury or less to provide a gradient for elimination

The influence of concentration of electrolytes on the brain under the condition of extracorporeal circulation has not been studied The electrolytes as constituents of the perfusing blood are not easily controlled inasmuch as they are subject to the continuous influence of the patient. There is evidence of a moderate degree of metabolic acidosis during perfusion which presumably is due to an increased production of fixed organic acids Incomplete studies of other electrolytic constituents suggest that there is no appreciable change in their concentration

An unwelcome constituent of perfusing blood is foreign material, be it bubbles fibrin clots silicone or any other particulate matter inadvertently introduced

Fries and his colleagues[6] recently have demonstrated the disastrous effects of introduction of oxygen into the carotid arteries of dogs The most pertinent features of this demonstration were that even minute quantities of the gas slowly introduced were capable of causing delayed recovery from anesthesia lethargy and death in eight to twenty four hours In all of the dogs surviving the injection of oxygen either gross neurologic defects were apparent clinically or cerebral damage was evident on postmortem study of those dogs killed later Avoidance of the hazard of bubbles requires that they be not created in the oxygenator or that they be dispersed before reaching the patient The possibility of micro-bubble formation from supersaturation of blood with oxygen at a temperature lower than that of the patient cannot be lightly dismissed Justifiably or not the criticism of bubble formation has been leveled at oxygenators which stream oxygen through a column of blood

The hazard of fibrin particles can be decreased by adequate heparinization design of cannulae and tubular junctions in such

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A neuropathologist has examined the tissues of the central nervous system of those patients who have died and on whom necropsy has been performed Review of his findings reveals that in one patient who was hemiplegic in the several hours between the operation and death an embolus consisting of a small bit of Ivalon sponge was found in the brain This of course cannot be related to perfusion per se In one other patient a number of focal infarcts were found scattered throughout the brain This patient lived sixty hours following attempted correction of severe infundibular pulmonic stenosis ventricular septal defect and common origin of the aorta and pulmonary artery from the right ventricle She had been alert until 24 hours after the operation at which time she became increasingly somnolent the occurrence of a neurologic incident at this time seemed likely The role of severe hemoconcentration as a cause of the thrombosis is suggested by the preoperative examination of blood which revealed a concentration of hemoglobin of 20 8 gm per 100 cc and a hematocrit reading of 77 per cent

No specific pathologic lesions have been found in the central nervous system of any of the remaining patients who have died and on whom postmortem examination has been made

In a previous presentation at this symposium[8] a syndrome of sudden death was described The basic pathophysiology of this syndrome has not been elucidated Brain damage cannot be implicated or eliminated as an etiologic factor The complete absence of evidence of neurologic damage in surviving patients and of neurologic lesions clearly due to extracorporeal circulation in nonsurviving patients and the elimination of the syndrome of sudden death in the most recent series of patients suggest that extracorporeal circulation can be accomplished without resulting neurologic damage

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2. Finnerty F A Jr Witkin L. and Fazekas J F Acute hypotension and cerebral hemodynamics preliminary report *M Ann District of Columbia* 22 115-116 167 1953

a fashion that turbulent flow is minimized, and finally by the presence of a filter in the arterial line[6]

EVIDENCE OF INCIPIENT OR REAL BRAIN DAMAGE

Evidence of incipient or real brain damage from extracorporeal circulation may be found during perfusion, in the postoperative period, and after death During perfusion the electroencephalogram is of value in assessing the adequacy of cerebral blood flow

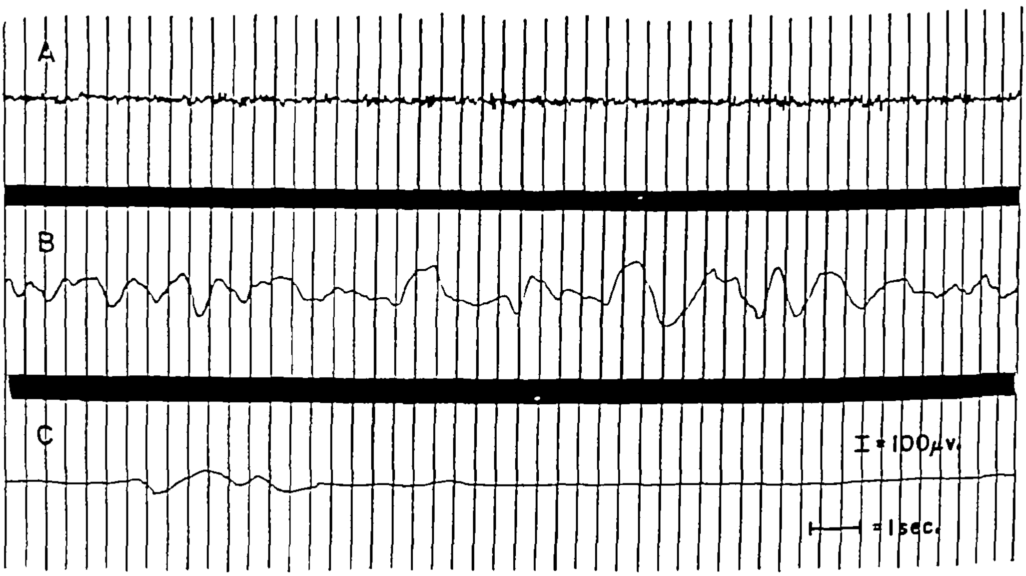


FIG 111 Electroencephalographic patterns *A* is characteristic of a light state of anesthesia with ether and is termed the "normal pattern" The pattern at *B* is seen with a reduction in cerebral blood flow and that at *C* with extreme reduction or absence of cerebral blood flow

Characteristic patterns are apparent at presumably normal flow and at seriously deficient flow[7] (Fig 111) We view with alarm the appearance of an abnormal pattern Such patterns occur infrequently and can usually be related to a recognizable and correctible cause In our experience an adequate perfusion is characterized by a normal electroencephalogram

In the postoperative period one might expect to find as evidence of brain damage extreme lethargy, coma, convulsions, mental aberration or focal neurologic signs Such signs have not occurred in any surviving patient of the 245 patients reported on in another paper at this meeting[5]

THE EFFECTS OF TOTAL CARDIOPULMONARY BY PASS PROCEDURES UPON CEREBRAL FUNCTION EVALUATED BY THE ELECTROENCEPHALOGRAM AND A BLOOD BRAIN BARRIER TEST

A Clinical and Experimental Investigation

By

PAUL C HODGES, M.D., ROBERT D SELLERS, M.D, JIMMY L STORY, M.D., PAUL H STANLEY, M.D., FERNANDO TORRES, M D., *and* C WALTON LILLEHEI, M.D

AT THE University of Minnesota Hospitals total cardiopulmonary by pass procedures have been routinely monitored in the operating room by means of a continuously recording electroencephalographic tracing utilizing a portable electroencephalographic apparatus with four scalp electrodes (Figure A) This procedure along with the measurement of the systemic blood pressure has proved to be particularly valuable as an index of the general well being of the patients during their by pass intervals The electroencephalogram is generally and quite correctly regarded as an accurate index of cerebral function and the brain in turn is a sensitive mirror of abnormalities due to hypoxia acidosis and

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1 The Graduate School, University of Minnesota.
2 Minnesota Heart Association
3. American Heart Association.
4 Life Insurance Medical Research Fund
5 National Heart Institute (H 630) USPHS
6 USPHS B-665(R)

3 Rosomoff, H L , and Holaday, D A Cerebral blood flow and cerebral oxygen consumption during hypothermia *Am J Physiol*, *179* 85-88, 1954
4 Stadie, W C , Riggs, B C , and Haugaard, N Oxygen poisoning *Am J M Sc*, *207* 84-114, 1944
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8 Kirklin, J W , McGoon, D C , Patrick, R T , and Theye, R A *What is adequate perfusion?* (In press)

co-operative than the younger age groups and provide a more rigorous test of the perfusion methods in terms of the total quantity of blood circulated

The second portion of this study related to the continuing in

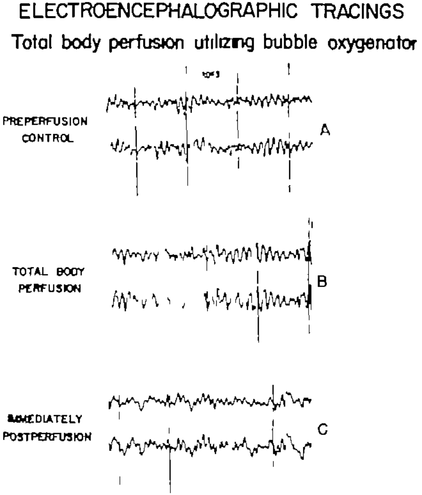


FIG B A typical operating room encephalogram obtained with this 4-electrode portable apparatus Case R R age ten years undergoing a thirty minute interval of total by pass employing the helix reservoir oxygenator at a flow rate of 56 cc of blood per kg body weight for repair of the atrioventricularis communis defects

vestigational work which has provided the basis of these clinical procedures In this phase of study we have sought for a more sensitive test than provided even by the electroencephalogram to aid us in evaluating refinements in heart lung machines as well as other

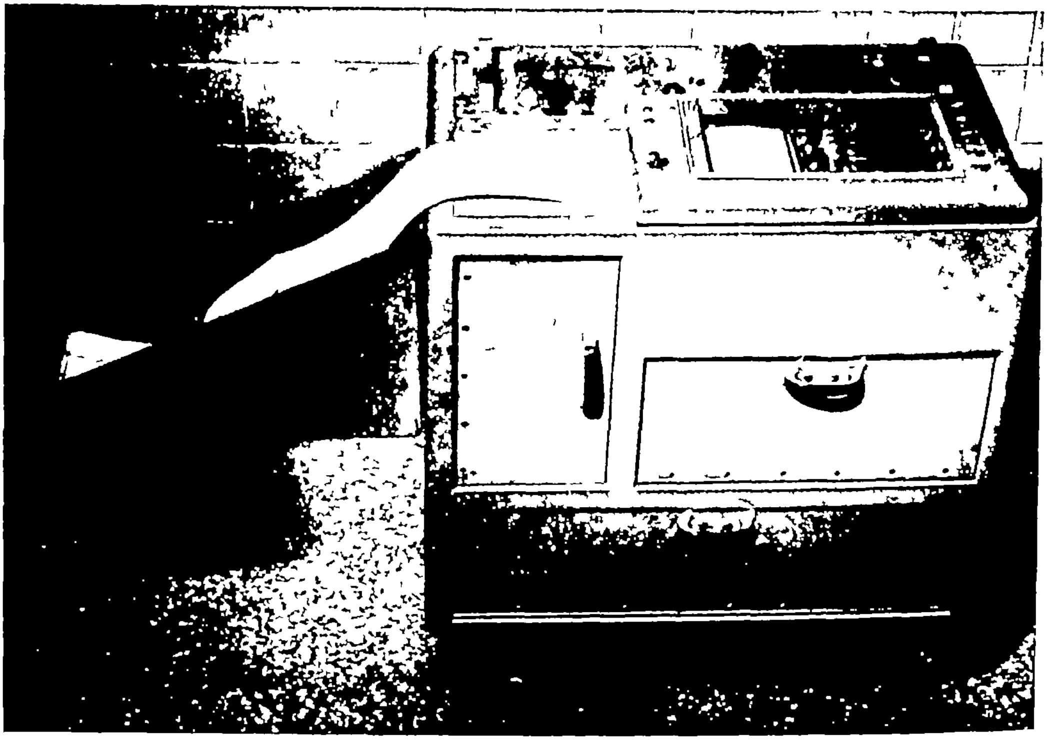


FIG A The portable electroencephalograph utilized in the operating room to *monitor cardiopulmonary by-pass procedures*

other aberrations during total body perfusion by an extracorporeal pump-oxygenator

With the refinement of total body perfusion methods, based upon increased knowledge and continuing experience, it has been amply demonstrated that the function of the heart and lungs can be temporarily taken over by an artificial heart-lung apparatus with the maintenance of life by total body perfusion, at a uniformly low risk [1] The brain wave pattern recorded in the operating room (Figure B) shows little change

It was deemed worthy of interest to study further a group of patients undergoing an interval of total cardiopulmonary by-pass for open cardiac surgery utilizing the helix reservoir pump-oxygenator Preoperative and again postoperative electroencephalographic recordings were carried out by the more sensitive 20-electrode apparatus in a shielded room free of any electrical interference

This more detailed electroencephalogic study has been carried out in older children and adults, since these patients would be more

co-operative than the younger age groups and provide a more rigorous test of the perfusion methods in terms of the total quantity of blood circulated

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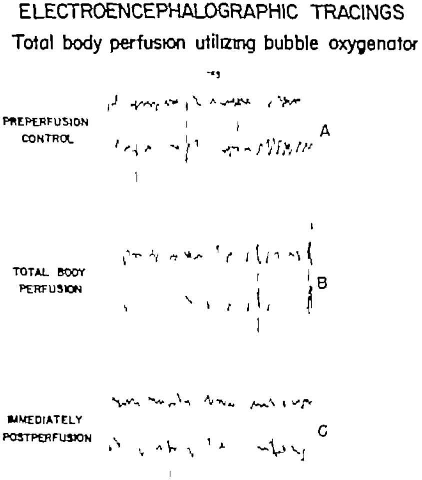


FIG. B A typical operating room encephalogram obtained with this 4-electrode portable apparatus Case R R age ten years undergoing a thirty minute interval of total by pass employing the helix reservoir oxygenator at a flow rate of 58 cc of blood per kg body weight for repair of the atrioventricularis communis defects

vestigational work which has provided the basis of these clinical procedures In this phase of study we have sought for a more sensitive test than provided even by the electroencephalogram to aid us in evaluating refinements in heart lung machines as well as other

aspects of the physiology of perfusion Attention has been directed primarily to the brain since, as mentioned, it appears to be the most sensitive of the vital organs In this search for a more critical index we have adopted a method developed by Moore[2] and widely used by neurologists and neurosurgeons in the localization of brain pathology This technic makes use of the fact that various of the vital dyes, which do not normally penetrate the blood brain barrier (abbreviated henceforth as B B B), will do so when this physiologic barrier has been disturbed by a wide variety of physical or chemical dyes One of the most useful of these dyes has been sodium fluorescin which penetrates the brain tissue from the blood following minimal breakdown of the B B B and is easily identified by its brilliant, yellow-green fluorescence when exposed to ultraviolet light Under ultraviolet light normal brain tissue has a definite bluish-grey hue if sodium fluorescin has been added to the animal's circulation prior to examination The hypophysis, choroid plexuses and area postrema fluoresce with a yellow-green hue while the remainder of the brain maintains its normal bluish-grey hue Fluorescence in other portions of the brain represents areas of breakdown in the normal B B B Moreover, this evaluation could be carried out in the intact animal or patient by use of tagged compounds (di-iodo fluorescin or radio- iodinated albumin) and a suitable counter, such as originally described by Moore[2]

METHOD OF STUDY OF THE BLOOD BRAIN BARRIER

The present investigation consists of a series of acute experiments performed on a total of 107 mongrel dogs believed to be in good physical condition at the time of experimentation Each animal, after an overnight fast, was premedicated with 15 mg morphine and 0 6 mg atropine one hour before light anesthesia was induced by intravenous administration of sodium pentothal (2½%) Thoracotomy, when utilized, was through the bed of the right fifth rib, and after the required attention to hemostasis the animals were heparinized with 2 mg heparin/kg of body weight A pair of venous cannulae were inserted through the right atrial wall into the superior and inferior venae cavae respectively The cavae were occluded around these cannulae by external occlusive

ligatures A single arterial cannula was placed in the left femoral artery In all animals in which perfusions were carried out, the Sigma motor pump* was utilized with the exception of the Group XIII animals in which the standard roller pumps supplied with the Mark Screen Oxygenator† were utilized Blood pressures when taken were recorded on a mercury manometer connected to a cannula placed in the opposite femoral artery Thirty minutes before termination of each experiment the animal received an intravenous injection of 25 mg /kg of body weight of 20% sodium fluorescein At the end of each experiment each animal was sacrificed by the intravenous administration of nembutal The brain was carefully removed for study under a mercury arc lamp with a Woods filter and then fixed in formalin for preparation of histologic sections

Donor blood used for priming of various oxygenators was freshly drawn into siliconized bottles containing 20 mg heparin per 500 cc

PLAN OF STUDY

Group I, Anesthesia Controls A series of five dogs weighing 6.8-12 kg was anesthetized in the usual manner following which each was given the usual dosage of sodium fluorescein and sacrificed thirty minutes later as described above The chest was not opened and no cannulae were placed

Group II Sham Operation Controls A series of seven dogs weighing 6 8-11 kg was subjected to anesthesia and various sham procedures A thoracotomy was performed on each dog in two animals caval cannulae were also placed in one a carotid cannula was placed and in two others the right carotid was ligated

Group III Hypotension Controls A series of five dogs weighing 7 11 kg was subjected to anesthesia as described The femoral artery and vein were cannulated the former in order to measure pressure and the latter to administer a diluted arfonad‡ solution in order to maintain the arterial blood pressure below 40 mm Hg for one hour

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* Sigmamotor Inc 3 North Main Street, Middleport New York
† G & K H art Lung Machin The Mark Co 31 West Street Randolph Mass
‡ Hoffman La Roche Inc

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The present investigation consists of a series of acute experiments performed on a total of 107 mongrel dogs believed to be in good physical condition at the time of experimentation Each animal, after an overnight fast, was premedicated with 15 mg morphine and 0 6 mg atropine one hour before light anesthesia was induced by intravenous administration of sodium pentothal (2½%) Thoracotomy, when utilized, was through the bed of the right fifth rib, and after the required attention to hemostasis the animals were heparinized with 2 mg heparin/kg of body weight A pair of venous cannulae were inserted through the right atrial wall into the superior and inferior venae cavae respectively The cavae were occluded around these cannulae by external occlusive

of body weight and cannulated through femoral artery and vein as previously described.[3]

Group IX, Disposable Sheet Oxygenator A series of twelve dogs weighing 10-20 kg was perfused for a period of fifteen minutes to two hours at flow rates of 35-70 cc /kg /min using the disposable type sheet oxygenator * Sigmamotor pump and gravity venous drainage with a plastic reservoir Each oxygenator was primed with 1250 cc of freshly drawn heparinized blood Six animals were cannulated in their femoral artery and in six of the animals the arterial cannula was placed into the right carotid artery

Group X, Disposable Sheet Oxygenator with Autogenous Lung Filter A series of five dogs weighing 9 6-16 kg in which the arterial cannula was inserted into the right atrium through the azygos vein Each was perfused by the sheet oxygenator for a period of one hour at a flow rate of 50 cc /min This experiment used the lung as a physiologic filter

Group XI Disposable Sheet Oxygenator With Nylon Screen Debubbler A series of thirteen dogs weighing 11.2 19 8 kg was perfused for periods of thirty minutes to one hour at flow rates of 50-60 cc /kg /min with the disposable type sheet oxygenator containing no antifoam In these units debubbling was accomplished by passing the arterialized blood through a fine mesh nylon screen

Group XII Rotating Drum Oxygenator A series of thirteen dogs weighing 10.2 16 8 kg was perfused for a period of one hour at flow rates of 45-60 cc /kg /min with a rotating drum film type oxygenator [4]

Group XIII, Screen Oxygenator A series of eleven dogs weighing 11 1 20.5 kg was perfused for a period of one hour at flow rates of 45-125 cc /kg /min on the Mark G & K heart lung machine Four of these were on the 16 screen unit seven on the 5 screen unit

Group XIV Helix Reservoir Oxygenator A series of nine dogs weighing 7 8-15 7 kg was perfused for periods of one to two

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* Travenol Laboratories, Morton Grove Illinois

Group IV. Air Embolism Controls. A series of three dogs weighing 6.5-10 kg. was anesthetized and one of the carotid arteries exposed in the neck. A measured quantity of air, consisting of 0.2 cc., 0.4 cc., and 0.6 cc. respectively, was injected into the carotid vessels. This air was administered by measuring the desired quantity of air in a tuberculin syringe, filling the remainder of the syringe with blood aspirated from the carotid artery. Without removal of the needle from the vessel this mixture was rapidly injected into the carotid artery. The animals were then sacrificed thirty minutes later.

Group V, By-pass (Pump) Controls. A series of five dogs weighing 8.6-13 kg. was perfused with an extracorporeal pump by-pass without oxygenator and without filters for a period of two hours at flow rates of 50-100 cc./kg./min. In four of these animals blood was shunted from the femoral to the axillary artery, while in the fifth animal the shunt was directly into the carotid.

Group VI, By-pass with Excess of Antifoam. A series of four dogs weighing 5.7-13 kg. was perfused with an extracorporeal pump by-pass system in which a reservoir containing an excessively heavy coating of Dow Corning Antifoam A had been interposed between the afferent cannula and the pump. In three of these animals the shunt was from femoral to carotid artery, while in the fourth the shunt was into the axillary artery. These animals were perfused for a period of two hours at flow rates of 65-100 cc./kg./min.

Group VII, Cerebral Angiography. A series of five dogs weighing 4-8 kg. was anesthetized in the usual manner following which 1 cc./kg. of 70% Urokon was rapidly injected into the carotid artery. These animals were then given sodium fluorescin and sacrificed in the usual manner. This experiment was intended to assess the sensitivity of the sodium fluorescin test in terms of a generally performed clinical study.

Group VIII, Controlled Cross Circulation. A series of ten dogs weighing 6.8-12 kg. was perfused a period of one hour at flow rates of 30-100 cc./kg./min. using cross circulation. Donors consisted of a group of ten dogs weighing 18.7-35 kg. which were anesthetized in the usual manner and given 2 mg. heparin/kg.

In Group I the normal control animals which were anesthetized by use of sodium pentothal for a period of thirty minutes all five dogs were normal to fluorescence

In Group II the sham operation control animals with anes thesia, thoracotomy and various cannulations all seven brains were negative to fluorescence

In Group III in which the animals were exposed to hypotension

TABLE I

SUMMARY OF RESULTS

	Study Group	*No of Dogs*	*Degree of Breakdown of Blood Brain Barrier*					
			Neg	*Trace*	*1*	*2*	*3*	*4*
Group I	Anesthesia Controls	5	5	0	0	0	0	0
Group II	Sham Operation Controls	7	7	0	0	0	0	0
Group III	Hypotension Controls	5	4	0	0	0	0	1
Group IV	Air Embolism Controls	3	1	0	0	0	0	2
Group V	By pass Pump Control	5	4	1	0	0	0	0
Group VI	By pass with Excess of "Antifoam A	4	0	0	0	0	0	4
Group VII	Cerebral Angiography	5	2	0	0	0	0	3
Group VIII	Cross Circulation	10	5	3	2	0	0	0
Group IX	Disposable Sheet Oxygenator	12	0	0	0	0	0	12
Group X	Disposable Sheet Oxygenator with Autogenous Lung Filter	5	5	0	0	0	0	0
Group XI	Disposable Sheet Oxygenator with Nylon Screen Debubbler	13	3	1	3	4	2	0
Group XII	Rotating Drum Oxygenator	13	1	6	3	3	0	0
Group XIII	Screen (Mark) Oxygenator	11	0	4	3	2	1	1
Group XIV	Helix Reservoir Oxygenator	9	0	2	5	0	2	0
	Total	107						

for one hour four dogs were without evidence of a breakdown of the B B B and one animal had a localized area of multiple punctate fluorescence classified as 4+

Group IV Air Embolism Controls In the animal receiving 0.2 cc of air directly into the carotid artery the brain was negative In the other two animals receiving 0 4 cc and 0 6 cc of air re spectively the brains were both 4+

In Group V the five animals in which the by pass shunts with pumps were performed but without extracorporeal oxygenation four dogs had brains negative to fluorescence The fifth was graded as trace on the basis of a single fluorescent area This last animal was perfused through an antifoam free plastic reservoir chamber

hours at flow rates of 50-70 cc/kg/min with the helix reservoir type oxygenator [1]

Grading

The brains from these animals, after careful removal, were washed under tap water, sectioned transversely in 4-6 planes and the cut surfaces examined under ultraviolet light The total number of fluorescent areas on the cut surfaces were counted and the brains graded on the following basis

No Fluorescent Areas	*Grade*
0	Negative
1- 3	Trace
4- 5	1+
6-10	2+
10-15	3+
16 or more	4+

Any brains which showed confluent areas of fluorescence larger than 2-3 mm in size were automatically placed in Group 4+

In the present study, fluorescence on the surface of the brain was disregarded, since its significance has not been elucidated

ENCEPHALOGRAPHIC STUDY OF PATIENTS UNDERGOING CARDIAC SURGERY

Ten consecutive adults or older children with cardiac lesions requiring open cardiotomy have had electroencephalograms recorded one or two days preoperatively by means of a 20-electrode apparatus in a shielded laboratory as described

Following the open heart procedure utilizing the helix reservoir pump-oxygenator these patients have been restudied as soon as they were essentially afebrile, free of any other significant complications, and could be safely moved to the EEG laboratory All electroencephalograms were interpreted by the neurologic consultant staff in charge of this facility

RESULTS

Blood Brain Barrier Experimental Studies

The results of these studies involving 107 dogs are summarized in Table I and are described individually for the respective groups as follows

In Group I the normal control animals which were anesthetized by use of sodium pentothal for a period of thirty minutes all five dogs were normal to fluorescence

In Group II the sham operation control animals with anesthesia thoracotomy and various cannulations all seven brains were negative to fluorescence

In Group III in which the animals were exposed to hypotension

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Group III	Hypotension Controls	5	4	0	0	0	0	1
Group IV	Air Embolism Control	3	1	0	0	0	0	2
Group V	By-pass Pump Controls	5	4	1	0	0	0	0
Group VI	By-pass with Excess of "Antifoam A	4	0	0	0	0	0	4
Group VII	Cerebral Angiography	5	2	0	0	0	0	3
Group VIII	Cross Circulation	10	5	3	2	0	0	0
Group IX	Disposable Sheet Oxygenator	12	0	0	0	0	0	12
Group X	Disposable Sheet Oxygenator with Autogenous Lung Filter	5	5	0	0	0	0	0
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In Group VI, the by-pass shunt through a chamber heavily coated with Antifoam A, all four brains were 4+ to fluorescence

In Group VII, the normal group of dogs having only a carotid angiogram, two brains were negative while three were 4+. Depth of anesthesia may have been a factor producing the wide variation in results The two negative brains were from deeply anesthetized animals while the three positive brains were from lightly anesthetized animals who were violently stimulated by the injection

In Group VIII, the controlled cross circulation perfusions, five brains were negative, three showed a trace, and two were 1+

In Group IX, using the standard type sheet oxygenator, all twelve brains were 4+

In Group X, animals utilizing the standard sheet oxygenator with arterial return into the right atrium so that the lung served as a filter, all five brains were negative

In Group XI, the standard sheet oxygenator with a mechanical or physical type of debubbler consisting of a nylon mesh in place of antifoam, three brains were negative, one trace, three 1+, and four 2+, and two were 3+

In Group XII, utilizing the rotating drum, film oxygenator together with the Sigmamotor pumps for total cardiopulmonary by-pass, one brain was negative, six trace, three 1+, and three 2+

In Group XIII, consisting of eleven animals perfused utilizing the Mark G & K pump oxygenator, four were trace, three 1+, two 2+, one 3+, and one 4+

In Group XIV, consisting of nine dogs perfused with the helix reservoir oxygenator with a light film of Dow Corning Antifoam A in the debubbling chamber as recommended,[1] two brains were trace, five were 1+, and two were 3+

Clinical Encephalography—Results

Of the ten consecutively studied patients, nine have been restudied following their intracardiac reparative surgery (Table II) All of these patients were alert mentally immediately postoperatively and free of any apparent neurologic sequelae Electroencephalography was carried out as soon postoperatively as they were essentially afebrile and could be safely moved to the testing

TABLE II

RESULTS OF ELECTROENCEPHALOGRAPHIC STUDIES PERFORMED UPON CONSECUTIVE ADULT PATIENTS UNDERGOING OPEN HEART SURGERY UTILIZING THE HELIX RESERVOIR PUMP-OXYGENATOR

Pat. No.	Age (Yrs)	Defect	Duration of Total Bypass Min	Perfusion Rate cc/kg	Electroencephalogram	
1	22	Aortic Stenosis	20	40	Preop	Normal
					Postop (12 days)	Normal
	13	Atrial Secundum Defect	20	31	Preop	Mildly Abnormal
					Postop (10 days)	Mildly Abnormal
					Postop (17 days)	Mildly Abnormal
3	18	Ventricular Defect	20	42	Preop	Normal
					Postop (5 days)	Normal
4	27	Atrial Secundum Defect	23	30	Preop	Normal
					Postop (29 days)	Normal
5	10	Mitral Regurgitation	20	30	Preop	Minimally Abnormal
					Postop (9 days)	Normal
6	22	Single Ventricle	62	30–35	Preop	Normal
					Postop (25 days)	Mildly Abnormal
7	20	Atrial Secundum Defect	16	30	Preop	Mildly Abnormal
					Postop (7 days)	Mildly Abnormal
8	31	Mitral Regurgitation	22	33	Preop	Normal
					Postop (10 days)	Normal
9	10	Tetralogy of Fallot	80	30	Preop	Normal
					Postop (14 days)	Normal

20 recording electrodes performed in a shielded laboratory

In Group VI, the by-pass shunt through a chamber heavily coated with Antifoam A, all four brains were 4+ to fluorescence.

In Group VII, the normal group of dogs having only a carotid angiogram, two brains were negative while three were 4+. Depth of anesthesia may have been a factor producing the wide variation in results. The two negative brains were from deeply anesthetized animals while the three positive brains were from lightly anesthetized animals who were violently stimulated by the injection.

In Group VIII, the controlled cross circulation perfusions, five brains were negative, three showed a trace, and two were 1+.

In Group IX, using the standard type sheet oxygenator, all twelve brains were 4+.

In Group X, animals utilizing the standard sheet oxygenator with arterial return into the right atrium so that the lung served as a filter, all five brains were negative.

In Group XI, the standard sheet oxygenator with a mechanical or physical type of debubbler consisting of a nylon mesh in place of antifoam, three brains were negative, one trace, three 1+, and four 2+, and two were 3+.

In Group XII, utilizing the rotating drum, film oxygenator together with the Sigmamotor pumps for total cardiopulmonary by-pass, one brain was negative, six trace, three 1+, and three 2+.

In Group XIII, consisting of eleven animals perfused utilizing the Mark G & K pump oxygenator, four were trace, three 1+, two 2+, one 3+, and one 4+.

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Clinical Encephalography—Results

Of the ten consecutively studied patients, nine have been restudied following their intracardiac reparative surgery (Table II). All of these patients were alert mentally immediately postoperatively and free of any apparent neurologic sequelae. Electroencephalography was carried out as soon postoperatively as they were essentially afebrile and could be safely moved to the testing

The hypotension controls are of interest inasmuch as it is well known that even at high flow rates approaching or equaling the basal cardiac output the systemic blood pressure of some patients drops significantly as they go onto the by pass If nothing is altered the systemic blood pressure often climbs steadily towards and may approach normal in the next thirty to sixty minutes The cause of this initial fall in blood pressure and the slowness of the body to adjust are not known by us at this time However it is of interest that profound hypotension for the intervals studied had relatively little effect upon the integrity of the blood brain barrier

Antifoam A has been widely used by virtually all workers in the field of open heart perfusions either within the oxygenator or in the cardiotomy return reservoir because it appears to be remarkably non toxic and non irritating to tissue even when directly implanted.[8] In this laboratory in the past similar studies designed to assay possible tissue toxicity of this substance have been carried out [8] and these have all been negative as well Thus the disturbance of the B B B in the Group VI animals in which blood for two hours was passed through a reservoir containing a heavy coating of this material emphasizes again that a very thin film of this material is all that should be used and preferably this should be baked on by autoclaving after application Filters and settling traps designed in an attempt to remove particulate antifoam have been unsuccessful, but decreasing the amounts of antifoam commensurate with actual needs has been successful.

The preponderance of positive results in the Group IX animals utilizing the sheet oxygenator were undoubtedly due to the excessively large quantities of antifoam that were contained in the debubbling chamber of these units and not due to air This conclusion is based upon the studies in Group X where the same oxygenator was utilized but the returning blood was filtered through the lungs first and in the Group XI animals in which the identical oxygenator was employed except for the elimination of Antifoam A and debubbling

These observations have opened up three other avenues of investigation now in progress First there is a wide variety of compounds of varying chemical structure which have antifoam proper

area In one patient (Case 6) the temporary presence of complete heart block in the immediate postoperative interval, requiring continuous pacemaker support, delayed retesting, and in another the presence of atrial flutter (Case 4) did likewise One patient died in the immediate postoperative interval before re-assay was possible

It is of interest that four (including the one patient who died) of these ten patients had abnormal electroencephalograms preoperatively In two of these there was no change postoperatively and in the third (Case 8) there was improvement toward normal This patient was in a terminal condition from chronic cardiac decompensation preoperatively, and it is likely that the abnormal electroencephalogram was a measure of her decreased cardiac output Postoperatively, the clinical improvement in her cardiac and physical status has been dramatic and no doubt the EEG improvement is a reflection of this change

One other patient with a normal preoperative EEG showed a mildly abnormal tracing 25 days postoperatively A subsequent retesting 6 weeks postoperatively showed a completely normal tracing Neither this patient nor the others with tracings considered abnormal preoperatively, had any clinically recognizable neurologic findings

DISCUSSION

This method of detecting alterations in the B B B , utilizing fluorescein and a Woods lamp may prove to be a useful test for experimental evaluation of perfusion technics and methods It has appeared to be a more critical index than the electroencephalogram However, even utilizing this delicate and sensitive test it is evident that disturbances in the B B B are not inherent in total body perfusions Anesthesia, thoracotomy, cannulations, and the shunting of large quantities of blood through the Sigmamotor pump for periods up to two hours gave consistently negative effects upon the integrity of the B B B On the other hand, even a tiny amount of air (0 4-0 6 cc) injected into the carotid arteries gave positive tests, as did cerebral angiography, as indicated by technics which are routine in most clinics

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DISCUSSION

This method of detecting alterations in the B.B.B., utilizing fluorescein and a Woods lamp may prove to be a useful test for experimental evaluation of perfusion technics and methods. It has appeared to be a more critical index than the electroencephalogram. However, even utilizing this delicate and sensitive test it is evident that disturbances in the B.B.B. are not inherent in total body perfusions. Anesthesia, thoracotomy, cannulations, and the shunting of large quantities of blood through the Sigmamotor pump for periods up to two hours gave consistently negative effects upon the integrity of the B.B.B. On the other hand, even a tiny amount of air (0.4-0.6 cc.) injected into the carotid arteries gave positive tests, as did cerebral angiography, as indicated by technics which are routine in most clinics.

The pre- and postoperative encephalographic studies which showed no significant alterations in the tracings made in a series of adult patients perfused for up to eighty minutes augment the clinical impression that the risk of carefully performed total body perfusions per se is not great and that the disturbances in bodily physiology are relatively minimal even in the present state of our knowledge

SUMMARY AND CONCLUSIONS

A sensitive test the blood brain barrier breakdown has been described as an aid for the evaluation of pump-oxygenators and in total body perfusion Several types of bubble and film oxygenators have been tested along with certain other pertinent variables in 107 dogs

In a series of adults and older children undergoing total body perfusions in the course of reparative intracardiac surgery for intervals of twenty to eighty minutes utilizing the helix reservoir oxygenator there were no significant alterations between the pre and postoperative electroencephalograms obtained by a multilead apparatus carried out in a shielded laboratory

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ties Some of these are naturally occurring substances known to be non-toxic Secondly, Antifoam A and probably other substances as well, have different affinities for the different materials on which they may be coated Lastly, antifoam agents can be eliminated entirely as illustrated by the results of the experiments in Group XI.

While admittedly the testing of the procedural set-up is a rather harsh one and possibly more than need be done as far as clinical perfusions of present durations are concerned, the only method of oxygenation that gave a majority of perfusions with negative or trace changes in the brains, was the use of controlled cross circulation This observation confirms a previously stated belief[7] that this beginning technic may still constitute the "standard" for comparison of other perfusion methods for some time to come

From the present study it is obvious that other factors can be important in producing breakdown of the blood brain barrier during perfusion Arterial spasm, which might be the presumed mechanism in the positive brains from three of the five animals in which carotid angiograms were performed, is a likely suspect Other obvious possibilities are the presence of particulate emboli in the form of fibrin, air bubbles, or even bits of coating material from the oxygenator itself Careful technic and design can exclude the possibility of air bubbles Protection from solid emboli depends upon the use of blood filters In all of these artificial oxygenator studies, arterial filters were utilized, but it is our opinion that considerable improvement in design of filters is needed

Studies of shunt by-pass, cross circulation, and various forms of oxygenation demonstrated the fact that cerebral disturbances, as measured by breakdown in blood brain barrier, can be avoided in total cardiopulmonary by-pass procedures, although in our results, unpredictable breakdown continues to occur

Temperature control is extremely important for all oxygenators whether of bubble, film, or membrane type Plasma, saturated with oxygen at low temperatures, will release oxygen bubbles if perfused into a patient or animal that is substantially warmer In all of these experimental studies, as well as the clinical perfusions, the oxygenator blood was kept either at the patient's body temperature or one to two degrees warmer, to obviate this occurrence

AIR EMBOLISM

By

VALLEE L. WILLMAN, M D., PANAGIOTIS ZAFIRACOPOULOS, M.D., *and* C ROLLINS HANLON, M.D

THE INFUSION of fluid into the arterial side of the circulatory system carries with it a risk of gaseous emboli, which may be lethal if they reach the brain When the infused fluid is mechanically-oxygenated blood, the risk of gaseous emboli is increased and, when the oxygenating mechanism is a "bubble oxygenator" the potential for gas embolism may be considerable

It has been suggested[1] that gas embolism is a likely cause of death in many of the animals dying after perfusion with blood from a bubble oxygenator Moreover Dennis group in their early laboratory experiences found that their oxygenator (not a bubble type) was delivering to the arterial side of the animal a small but constant stream of gas bubbles In subsequent investigations they have simulated the clinical picture of neurologic damage sometimes seen after use of an oxygenator by deliberate injection of gases into the carotid artery of the anesthetized dog Introduction of air in volumes of 1 5 to 3 ml. per kg of body weight over a period not exceeding 1 minute resulted in immediate evidence of neurologic damage despite anesthesia Fourteen of sixteen dogs so treated did not survive and evidences of neurologic deficit were present in two survivors after three months When air was injected into twenty nine dogs over a period of one hour in amounts from 0 33 to 2 0 ml per kg the immediate evidence of air embolism was often negligible but twenty of these animals died within a day of the experiment and all of the nine survivors had evidences of neurologic damage Injection of oxygen instead

From the Department of Surgery St Louis University School of Medicine The investigation was supported in part by a research grant (H 2558) from the National Heart Institute of the National Institutes of Health, Public Health Service and by a research grant from the St Louis Heart Association

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The infusion of fluid into the arterial side of the circulatory system carries with it a risk of gaseous emboli which may be lethal if they reach the brain. When the infused fluid is mechanically-oxygenated blood, the risk of gaseous emboli is increased, and when the oxygenating mechanism is a "bubble oxygenator," the potential for gas embolism may be considerable.

It has been suggested[1] that gas embolism is a likely cause of death in many of the animals dying after perfusion with blood from a bubble oxygenator. Moreover, Dennis' group in their early laboratory experiences found that their oxygenator (not a bubble type) was delivering to the arterial side of the animal a small but constant stream of gas bubbles. In subsequent investigations they have simulated the clinical picture of neurologic damage sometimes seen after use of an oxygenator by deliberate injection of gases into the carotid artery of the anesthetized dog. Introduction of air in volumes of 1.5 to 3 ml. per kg. of body weight over a period not exceeding 1 minute resulted in immediate evidence of neurologic damage despite anesthesia. Fourteen of sixteen dogs so treated did not survive and evidences of neurologic deficit were present in two survivors after three months. When air was injected into twenty-nine dogs over a period of one hour in amounts from 0.33 to 2.0 ml. per kg., the immediate evidence of air embolism was often negligible, but twenty of these animals died within a day of the experiment and all of the nine survivors had evidences of neurologic damage. Injection of oxygen instead

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of air did not materially alter the incidence of injury to the nervous system, although the severity of symptoms and the death rate were decreased. These workers emphasized the fact that, even in animals which survived without clinical neurologic abnormality, one could demonstrate pronounced cerebral damage by histologic techniques. They felt that a reappraisal of current pump oxygenator technics was indicated.

A similar warning note was sounded in the presentation of Maloney[2] on the basis of comparative survival rates in dogs with high and low flows for a period of twenty minutes using the bubble oxygenator. With flows at 35 ml. per kg. of body weight survival rate was 41 per cent, at 70 ml. per kg. there were no survivors. When the period of perfusion at the lower flow rates was raised to forty minutes, there were no survivors. It appeared possible that increasing amounts of a "toxic element" might have been introduced into the animals by increasing the flow rate or duration of perfusion. Many of the animals died in a state characterized by areflexia and hypotension consistent with cerebral damage, and these investigators thought that minute amounts of gas suspended in the perfused blood might be the causative "toxic element." Using two oxygenators in parallel there was survival of three out of ten animals perfused at an aggregate flow of 70 ml. per kg. Without claiming statistical significance for this survival rate, they did point out that these were the only survivors among twenty-four dogs on "high" flow rates with the bubble oxygenator in their laboratory.

The studies presented by Maloney and his colleagues emphasize the high mortality in experimental animals with the bubble oxygenator. The evidence that such mortality is due to microscopic air embolism is admittedly inferential, and there are many possible causes of the diffuse cerebral damage which underlies certain deaths during the first day after extracorporeal perfusion.

It has not been demonstrated that the areflexic, hypotensive animal that fails to awake from perfusion is a phenomenon peculiar to the bubble type of oxygenator.

Moreover, there is inadequate information available concerning the use of bubble, film and membrane type oxygenators by the

same group of investigators It is unreliable to compare the results of one group with those of another using the same basic bubble oxygenator since as Lillehei has stated the DeWall oxygenator is so simple that the urge to modify it is almost irresistible With certain apparently trivial modifications however the performance of the oxygenator may be substantially altered and lethal complications attributed to a basic defect in oxygenator design may possibly be due to the secondary modifications

By injection of air or oxygen into the carotid arteries of dogs Dennis group has simulated closely the clinical and histologic picture in certain animals which fail to survive extracorporeal circulation It has not been demonstrated directly however that the deaths in Dennis animals and in those which do not survive extracorporeal circulation with the bubble oxygenator are due to the same cause

In an effort to elucidate the role of gaseous embolism in deaths associated with use of the bubble oxygenator we have perfused the brain of dogs with blood from a DeWall type III pump oxygenator This permits study of the brain as a filter for potential emboli, while the remainder of the animal is maintaining relatively normal circulation without extracorporeal assistance

METHODS

Mongrel dogs 9 to 27 kg in weight were anesthetized with sodium pentothal intravenously Repeated small doses were given to prevent struggling An endotracheal tube was placed and compressed air was delivered into it by a mechanical interrupter Sterile surgical technic was employed and the perfusion apparatus was sterilized by autoclaving All animals received 500 mg of tetracycline in 500 ml of physiological saline by intravenous infusion during the first ninety minutes of the experiment The survivors received penicillin 400 000 units on the first postoperative day Heparin was given intravenously in a dosage of 2 mg per kg before placing the catheters for perfusion

In ten animals blood from a femoral artery was passed through the electrode chamber of a constantly recording pH meter and returned to the femoral vein Femoral artery pressure was re

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ml per minute the amount returned to the apparatus varied from 1050 to 1420 ml per minute Oxygen flow to the bubbling column was 4 to 5 l per minute At least 1000 ml of blood was kept in the helix reservoir The perfusion period lasted 120 minutes in three animals and 180 minutes in two animals After perfusion protamine was given in a dose of 2 mg per kg the carotid arteries were ligated (see Figure 112)

Group II

In eight animals ranging in weight from 9 to 20 kg the subclavian arteries were ligated intrathoracically at their origins several days before the perfusion During perfusion, blood was with

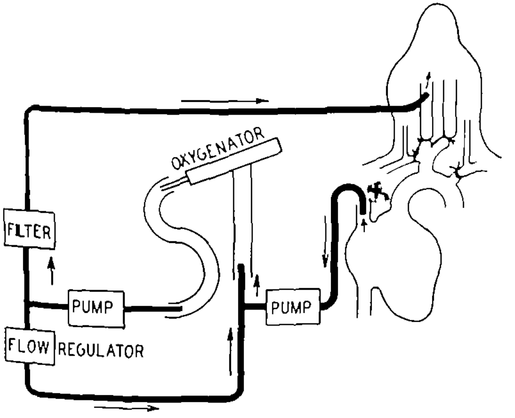


Fig 113 Diagram of extracorporeal circulation in animals of group II (Willman)

drawn from the superior vena cava and delivered to a DeWall pump oxygenator model III The oxygenator was operated at rates of 1100 to 1400 ml per minute Oxygen flow to the bubbling column was 4 to 5 l per minute At least 1000 ml of blood were

corded constantly as was pressure in one of the carotids being perfused Electrocardiograms and vertex-occiput electroencephalograms were recorded intermittently

Group I

In five animals whose weights varied between 13 and 27 kg, blood was withdrawn from the inferior vena cava for oxygenation by a pump oxygenator of the DeWall type, model III The pump oxygenator was operated at flows of 1100 to 1500 ml per minute The output from the arterial side of the apparatus was divided into two parts, a smaller fraction being delivered to the animal and the majority being recirculated through the oxygena-

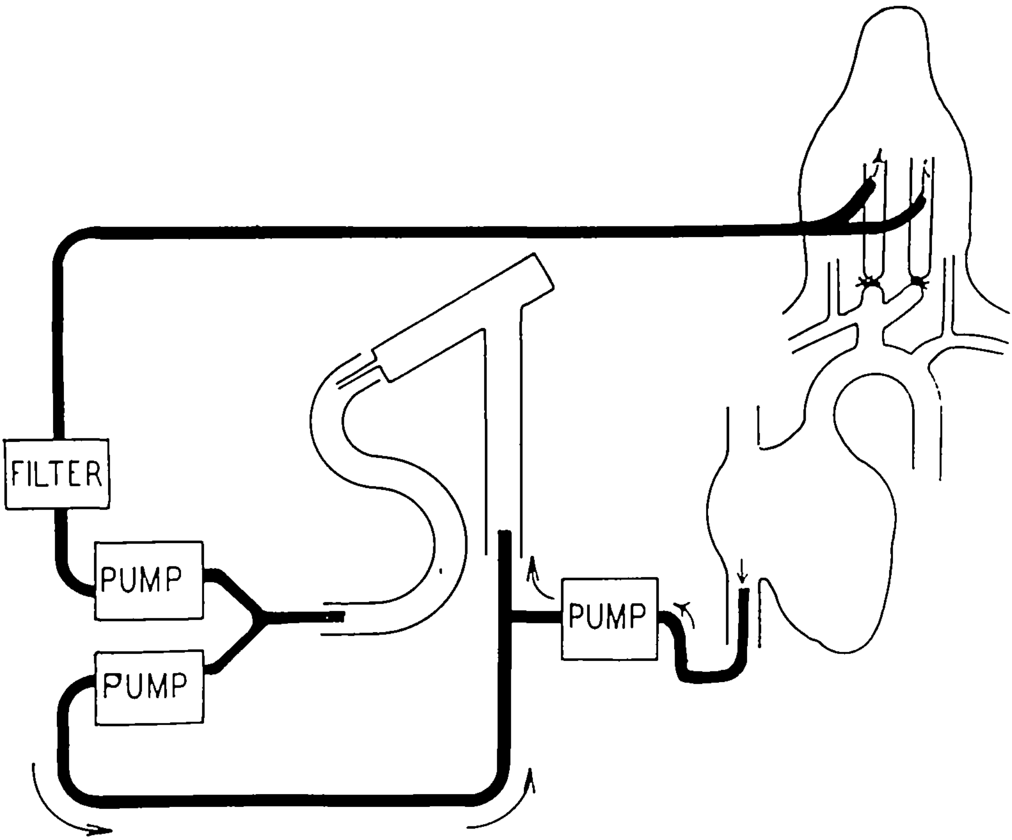


FIG 112 Diagram of extracorporeal circulation in animals of group I (Willman)

tor The animal was perfused through two small catheters directed cephalad in the carotid arteries and secured by ligatures which prevented flow to the carotids from the aorta The amount of blood delivered to the carotid arteries varied between 55 and 75

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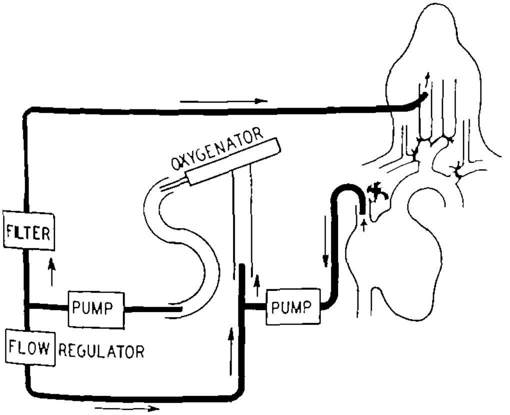


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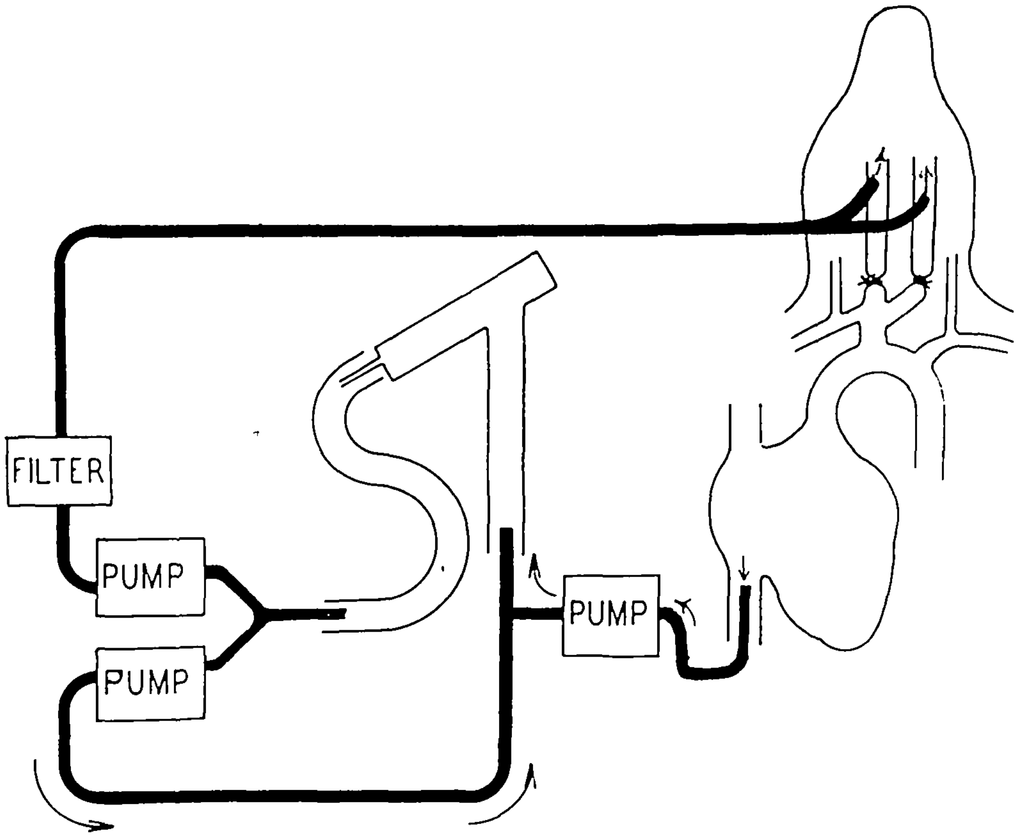


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eye for a period of several days with subsequent return of vision It was felt that the changes in this group of animals were associated with perfusion by volumes far in excess of normal cerebral flow

In ten instances in which the pH of arterial blood was measured, there was little alteration during the two hour perfusion There were no elevations the maximum depression was 0 1 below the initial pH

DISCUSSION

The results in these experiments demonstrate that perfusion of the dog s brain with blood from a bubble oxygenator for periods up to three hours may be accomplished without mortality or gross neurologic sequelae These results have been attained in only a small series of animals at flow rates comparable to normal canine cerebral blood flow These flows equal the expected amount of blood to the head during total extracorporeal circulation

If the perfusate from a bubble oxygenator contains gaseous or particulate emboli and if these are the cause of the severe cerebral damage sometimes seen with use of pump oxygenators one might expect the animals in Group I to show these neurologic sequelae In preliminary studies of this small group such cerebral damage is not apparent However when perfusion is carried out at rates far beyond the normal cerebral flow there is a high incidence of serious or lethal neurologic damage Such damage occurs at these flow rates even when the oxygenator is removed from the perfusion system

Although it is highly unlikely that such overperfusion plays any part in the unexplained deaths associated with extracorporeal circulation it is apparent that nearly identical neurologic patterns may be produced by many different types of insult to the brain Injection of particulate matter or gas bubbles into the carotid artery will produce such a pattern of injury but proof is lacking that gaseous emboli are the actual causative agent in deaths following perfusion with a bubble oxygenator

Clowes and others have commented on the difficulty of detecting fine bubbles in blood by the usual physical means and suggested the application of an ultrasonic flowmeter in such attempts

kept in the helix reservoir The animals were perfused for 120 minutes through a 10 F catheter directed cephalad in the right carotid artery There was no flow through this vessel from the aorta The left carotid artery was occluded during the perfusion Flow through the right carotid artery was regulated so as to keep the carotid pressure at or above the pressure in the femoral artery The carotid pressure never exceeded the femoral pressure by more than 20 mm Hg Carotid flow amounted to 15 to 20 ml per kg body weight per minute, this is contrasted with a flow of approximately 3 to 5 ml per kg per minute in the animals of Group I

Of the total output from the oxygenator, 150 to 300 ml per minute perfused the carotid artery, the remaining 1000 to 1200 ml were recirculated to the oxygenator After perfusion was completed, protamine was given in a dose of 2 mg per kg The opening in the right carotid artery was repaired with arterial sutures (see Figure 113)

RESULTS

Group I

All five of these animals survived During perfusion there was slight reduction in voltage of the electroencephalogram but no gross alteration in pattern These animals required repeated administration of anesthetic agent during the perfusion to prevent struggling They awoke promptly after perfusion with good muscle tone and normal reflexes

Four of these animals were sacrificed at intervals up to 15 days after perfusion No gross changes were noted in the brain and detailed pathologic studies will be reported later.

Group II

Four of these eight animals failed to awaken Three died within twelve hours, and one after six days The four that recovered demonstrated normal behavior None awakened and later died In all eight instances there was depression of voltage in the electroencephalogram during the perfusion

In the four animals which died, as well as in two of the survivors, there was proptosis of the right eye and edema of the right side of the face This was a striking finding In the two survivors with this condition there was blindness in the edematous

DISCUSSIONS

DR. EISEMAN Denver We have been particularly interested in the basic hydrodynamic principles that account for the impedance of blood flow during air embolism In hydraulics a flowing column of fluid interrupted by a column of gas is called a slug flow system Surprisingly little is known about the flow characteristics of slug flow Engineers have concentrated on the characteristics of foams and fluids containing air bubbles smaller than the diameter of the containing tube since such systems are of commercial importance but the properties of slug flow have been almost totally neglected

Jamin, in 1860 reported that slugs of air impede fluid flow but Smith, in 1930 showed that there was no such resistance in a scrupulously clean tube without constriction We have confirmed Smith's findings in tubes of a constant diameter regardless of the number or size of the bubbles We have also found that in tubes of narrowing diameter or containing constrictions air bubbles do not impede flow as long as the column of fluid and air remain in motion This I might add, was unexpected and difficult to believe but it is true If however the column of fluid is stopped with the bubble at the point of constriction a different set of forces pertain (hydrostatics not hydrodynamics) and the air slug offers a very significant resistance to flow In the course of its pulsatile flow blood goes through such a stationary phase and therefore these hydrostatic forces are applicable to *in vivo* air embolism When an air bubble is thus hung up at a constriction pressure far in excess of the original propulsive force is necessary to push it through the narrowing and to resume fluid flow Indeed under some conditions the proximal convex fluid-air meniscus may be bent inward, i e reversed before the bubble pops through the constriction

I will not further belabor the dynamics of such a system except to say that we have found that resistance to flow is directly proportional to the surface tension of the fluid Lowering surface tension decreases resistance to flow We have applied this principle to the experimental animal with coronary air embolism produced by the left intraventricular injection of known doses of air To date more than 150 dogs have been so studied and we have found that a 100% fatal dose of air can be reduced to an LD 45 if a minute amount of surface tension lowering substance is injected simultaneously with the air We have further shown that this protective effect is proportional to the degree of surface tension depression of the blood

Various surface active agents have been tested but Tween 80 and

We have had no experience with ultrasonic detection of bubbles in blood but are employing other physical means such as the exposure of blood to a vacuum as described by Harvey.[4]

Experiments are in progress to assess the possible role of hypersaturation of blood with oxygen as a detrimental factor in extracorporeal circulation. The possibility of deleterious effects of abundant oxygen supply in the cooled state was suggested in 1953 by Clark, Helmsworth and associates.[5] More recently Penido, Swan and Kirklin[6] have commented on the possibility of damage from excessively high oxygen tension of arterial blood in connection with studies using a bubble type oxygenator.

The precise role of gaseous embolism in the neurologic complications after use of pump oxygenators requires further study.

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DISCUSSIONS

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formed on 12 dogs and the results are essentially as follows Cerebral flow which was measured by a continuously recording magnetic rotameter was found to have a linear relationship to central aortic blood pressure but had a variable and unpredictable relationship to perfusion rate In addition cerebral oxygen consumption was likewise related to cerebral blood flow in a linear fashion Perhaps the most interesting observation made during these experiments however was that irrespective of flow rates employed cerebral oxygen consumption decreased significantly during extracorporeal circulation In most instances it was only about 50 per cent of control values We are unable to explain this phenomenon since arterial oxygen tension was within relatively normal limits and no significant variation in pH occurred These experiments suggest that cerebral blood flow is severely reduced during extracorporeal circulation using basal perfusion rates and that under certain circumstances cerebral hypoxia may develop

DR. JAMES V MALONEY Los Angeles In regard to Dr Hanlon s comments about our modification of the bubble oxygenator I would like to point out that these modifications were the same as those added by DeWall and associates subsequent to their original publication. We were disappointed by the experimental mortality Dr Hanlon alluded to and therefore developed four methods to determine if microscopic air embolism was the cause of this mortality The first method consisted of observation through the microscope of a glass capillary tube placed in parallel with the arterial line We could identify globules of foreign material but could not tell if they were air or antifoam compound. The second method developed by Mr Arzouman in our laboratory consisted in sampling blood from the aorta in sealed capillary tubes during perfusion. These capillary tubes were then incubated at body temperature in the upright position for a period of thirty minutes Air bubbles varying in size from 600 to 900 microns in diameter could easily be demonstrated. These bubbles were always present at blood gas ratios in excess of 1 7 occasionally present at blood gas ratios of 1-6, and rarely present at ratios of 1-5 The bubbles are illustrated in this slide (figure not reproduced) The third technic for the demonstration of air bubbles consisted in inserting what engineers call a "plenum chamber" in the arterial line We were able regularly to trap large numbers of exceedingly small bubbles in this chamber Masses of such bubbles are illustrated at the top of the plenum chamber in the next slide (figure not reproduced) The fourth method was a modification of Schubert s negative pressure fixation technic de

Dow-Corning Antifoam A or B seem most suitable because of their effectiveness in lowering surface tension of blood and their relative lack of toxicity As most of this audience knows, Dow-Corning Antifoam A is a particulate silicone and its direct intracardiac injection, even in minute amounts, is not desirable Unfortunately, we have not found any other non-particulate surface active agent that is equally effective

There are many obvious practical implications of these experimental findings as they relate to pump oxygenators First, they suggest that antifoam agents may have an effect on air emboli beyond merely cutting down the number and size of bubbles in our machines Second, the difference in the impedance to flow produced by air emboli during continuous perfusion contrasted to that found during a pulsatile flow should be mentioned According to our hydraulic studies, resistance would be minimal during a constant flow or perfusion and the effect of air emboli might not become evident until the pulsatile flow of the normal heart beat is resumed

Little new has been added to our knowledge of air embolism for many years and it would seem that a review and further study of the basic hydraulics of this condition is in order

DR SAMUEL KAPLAN, Cincinnati With the use of the polarographic technic, we have measured the tissue oxygen tension in the brain of dogs under varying conditions of cerebral circulation (*J Thoracic Surg* 32 576, 1956) In normothermia the oxygen availability to the brain drops immediately and precipitously after occlusion of the inferior and superior vena cava with the flow through the azygos vein left intact (azygos principle) Equivalent polarographic readings were obtained when the intact animal was ventilated with a mixture containing about 10 per cent oxygen It is concluded that during low flow rates oxygen availability to the brain is significantly reduced and may approach levels only slightly in excess of those resulting in brain hypoxia

DR OSCAR CREECH, JR, New Orleans During the past year we have had three patients who developed neurologic disturbances following open intracardiac surgery under extracorporeal circulation Each of these patients was perfused at relatively low flow rates and the clinical manifestations suggested hypoxia as the cause of the neurologic complications Therefore, some experiments were carried out to measure cerebral blood flow and oxygen consumption during extracorporeal circulation using a bubble oxygenator These experiments were per-

biopsy specimens were then placed in a negative pressure chamber and subjected to one half atmosphere of negative pressure The rationale of this experiment is that if any microscopic air emboli was present it should obey Boyle s law expand and thus become easily visible on a microscopic section Two strange things occurred when the tissues were exposed to one-half atmosphere negative pressure The control biopsies and those taken during the use of a Gibbon oxygenator remained quietly at the bottom of the pressure chamber Those tissue specimens taken during perfusion with the bubble oxygenator behaved as Cartesian divers and floated to the surface where they remained so long as the negative pressure was applied to the surface of the formalin Secondly these tissue specimens effervesced like an Alka seltzer tablet After four days of fixation in formalin at the high negative pressure routine histologic sections were made Slide 3 (not shown) shows a control specimen Figure 114 is a section from the liver of a dog perfused at a flow rate of 70 ml per kilogram body weight at a blood gas ratio of 1 to 10 Scores of microscopic air emboli are demonstrated Of these four technics the most sensitive was the plenum chamber method which permitted demonstration of air embolism with blood gas ratios as low as 1 to 3

Before adopting the Gibbon pump-oxygenator for clinical use at our clinic we employed the bubble oxygenator for a period of 9 months with a modicum of success Numerous other investigators have used the bubble oxygenator with good results witness the beautiful results shown by Dr DeWall yesterday It is therefore hard to determine the meaning of these experimental studies Perhaps the studies indicate that dogs do not tolerate air embolism as well as patients

DR KARL E KARLSON Brooklyn The experiences which we have had with respect to air embolism have been mentioned by Dr Patrick and by Dr Hanlon. We have been trying to reproduce the post perfusion syndrome which we have seen in animals after perfusions suspected of producing air embolization. By injecting air or oxygen into the internal carotid artery of the dog this syndrome can be reproduced It took about twice as much oxygen as air to do this The findings which were uniform were (1) the depth of anesthesia was increased and (2) there was always cerebral damage at autopsy either after death or sacrifice of the animals which did recover normally There was a large range of abnormal findings between normal recovery and death

Subsequently Dr Fries Dr Kaplan and I have repeated these experiments injecting 0.25 cc of air into the right internal carotid artery of the

veloped by Dr Karl Schmutzer in our laboratory This method consists in taking tissue biopsies of liver, kidney, and brain of an experimental animal before and during perfusion with the bubble oxygenator These



FIGURE 114 (Maloney)

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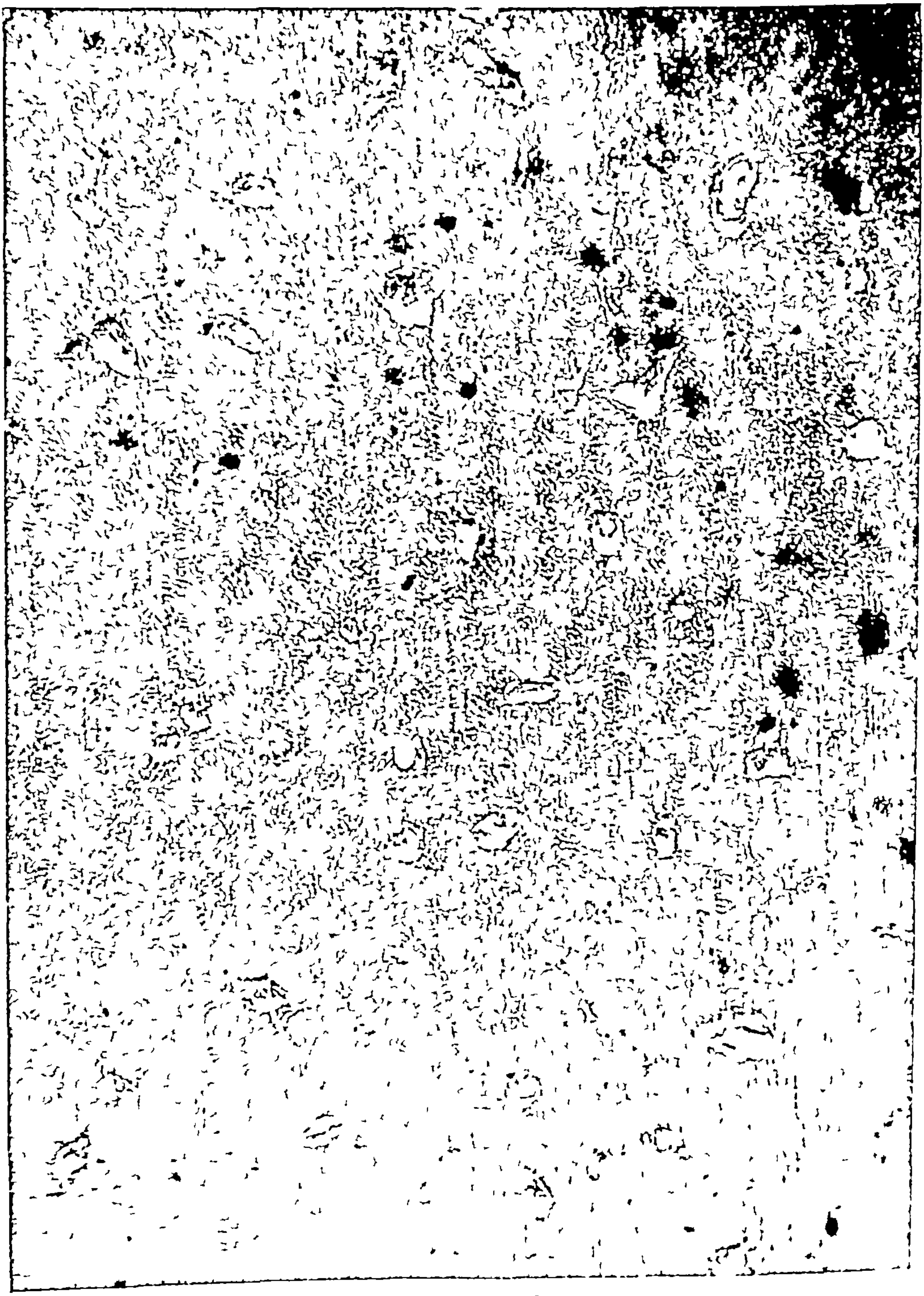


FIGURE 114 (Maloney)

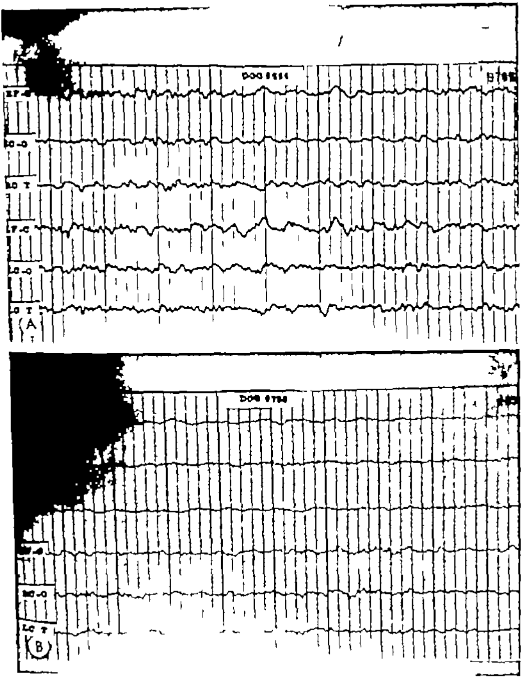


FIGURE 116 A & B

dog per minute over a period of one hour a total of 15 cc of air This produced the same range of cerebral damage we have described previously Electroencephalograms were recorded continuously before during and for a period after this air injection We found some E E.G s

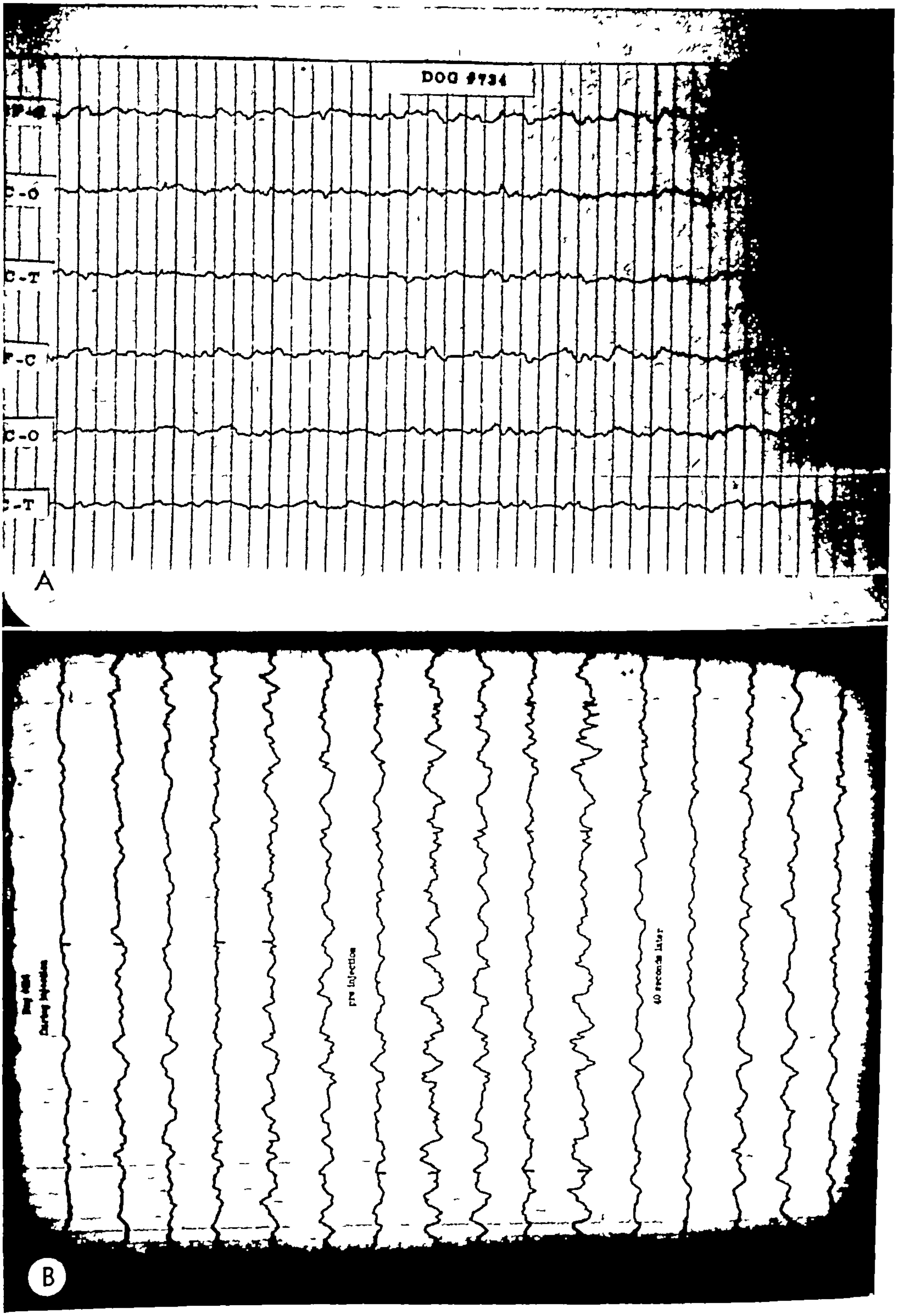


FIGURE 115 A & B

blood from swishing back and forth through the filters may also be of considerable importance

Thank you

DR JERE W LORD JR New York In our laboratory beginning with the bubble oxygenator patterned after Dr DeWall's a step-by step simplification of the oxygenator took place until the apparatus shown in the first slide (Figure 117) was utilized. Seventy-one per cent of the animals survived runs from 20 to 70 minutes with some sort of open cardiotomy Of those that succumbed post perfusion, there were several which expired without obvious reason within 48 hours In none of the runs were macroscopic bubbles seen through the Tygon tubing

In an attempt to develop a single and effective bubble monitor we have constructed the apparatus shown in Slide 2 (Figure 118) This is a polyvinyl plastic frame the chamber of which is 6′ long, 2′ wide, and 1/64″ thick so that the cross sectioned one is equal to the ¼ Tygon tubing used in the circuit. The monitor has been placed in a circuit consisting of an oxygenator Sigmamotor pump and tubing and various flow rates studied. Monitoring may be carried out during flow or by

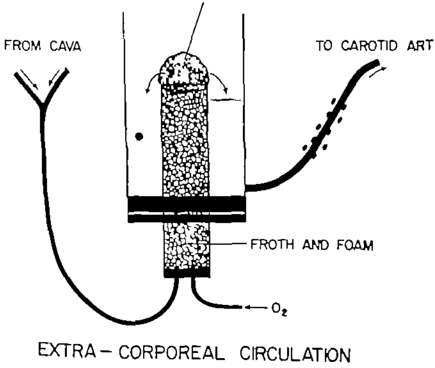


FIGURE 117 (Lord)

showed no change or very slight transient change, some of those animals died and some recovered However, some electroencephalograms showed gross changes, particularly on the right side, again, some of these animals died and some recovered apparently normally

In Figure 115A is a normal E E G after injection of 15 cc of air This dog recovered and appeared normal Figure B shows a more complicated experiment, but the normal pre-injection E E G on the center six lines are seen The only change we could find throughout an hour's continuous run during air injection was a little change on the right side which lasted only the length of one page of the paper (upper six lines) It became normal again within forty seconds (lower six lines) This dog died without recovering consciouness Figure 115B, from the record of another animal, shows an E E G which had definite changes on the right These occurred about six minutes after injection started This dog lived and appeared normal Figure 116A & B shows the most profound E E G change we have encountered with air injection The top three lines are from the right side and the bottom three from the left They all show changes from the preinjection E E G , most striking on the right This dog died

We feel, on the basis of these studies, that the E E G does not reflect accurately the presence or amount of cerebral arterial air embolism and is not a satisfactory basis for predicting the clinical abnormalities which will follow in the dog These findings will be of interest to those who are using E E G tracings in conjunction with heart-lung machines in the laboratory to evalute their effects on dogs Whether these findings can in any way be translated to humans remains to be seen

DR CHARLES K KIRBY, Philadelphia When we reported our experiments on brain embolization associated with the bubble oxygenator at the American Association for Thoracic Surgery meeting here in Chicago three or four months ago, we had no evidence that the emboli were due predominantly to gas bubbles, to particles of fibrin or anti-foam, or to something else Subsequent studies have not, as yet, clarified the nature of the emboli significantly We appreciate the opportunity of stating again that a bubble oxygenator appears to be relatively safe at the flow rates we mentioned if properly used, that is, if an open reservoir with a large surface area and a long vertical column beneath it is interposed between the arterial filters and the arterial pump It seems likely that the potential emboli collect on the surface of the reservoir, and the depulsating effect, which prevents

which the whole brain is fixed in a vacuum the vacuum being in the realm of 300 mg Hg Gas bubbles present in it will expand to immense proportions

Figure 119 Here is the brain of a dog subjected to air embolism by injection of air in the carotid artery to the extent of 0 25 cc per kilo of body weight The brain shows large cyst like vacuoles throughout the



FIGURE 119 (Heimbecker)

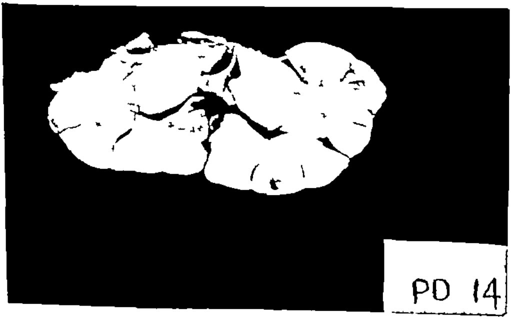


FIGURE 120 (Heimbecker)

stopping the flow and scanning with a dissecting microscope with magnification of twenty to sixty times The monitor can be placed on a side-arm so that perfusion need not be interrupted A fluorescent light is placed beneath the chamber

With flow rates up to 900 cc/min, no bubbles were seen when scanned with the naked eye However, with magnification of sixty times

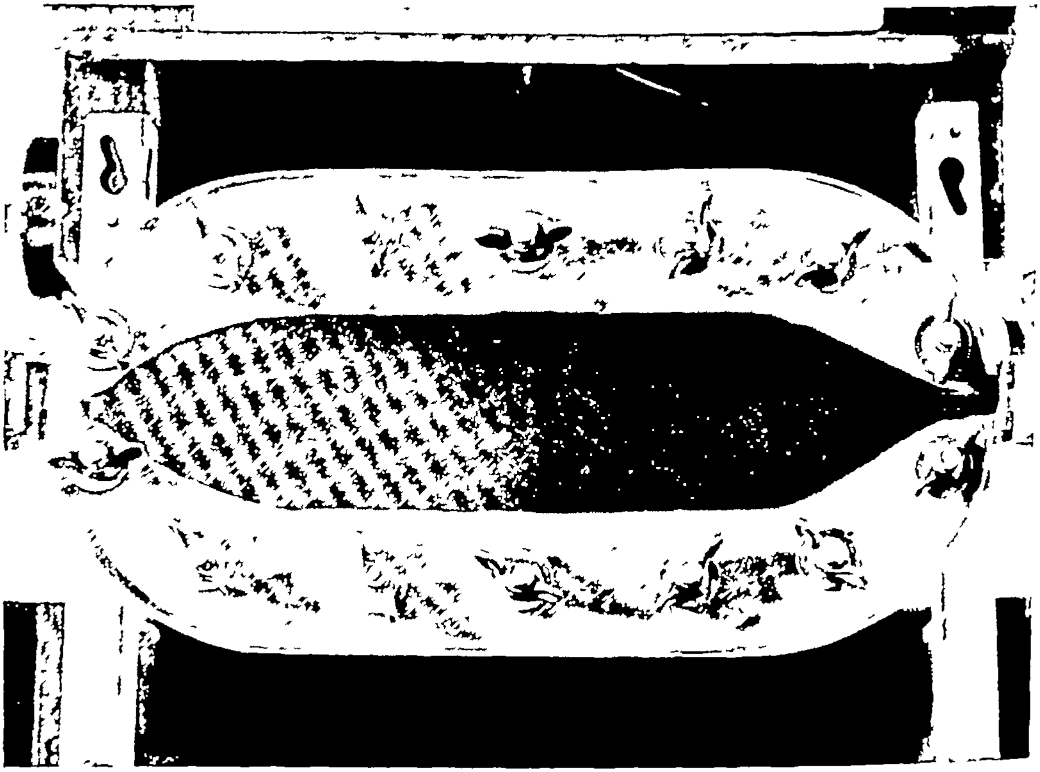


FIGURE 118 (Lord)

flow rates of 500 to 900 cc/min showed an average of 3 bubbles per field At a flow rate of 1200 cc/min, an average of 125 bubbles per field could be counted in the chamber when scanned through the microscope with the flow interrupted No bubbles were visible during flow either in the chamber or in the Tygon tubing

A run of two hours employing the Bolton bubble oxygenator at a flow rate of 1000 cc/min —no bubbles were to be seen by scanning the chamber with the circulation interrupted

We believe that this bubble monitor may be of value in detecting microscopic bubbles which could be responsible for some aspects of cerebral damage

DR RAYMOND O HEIMBECKER, Toronto, Canada We in Toronto have studied a technic originally described by Schubert in

EFFECTS OF EXTRACORPOREAL CIRCULATION ON RENAL FUNCTION

By

GEORGE C. MORRIS, JR., M.D., WILLIAM C. AWE, B.S., HARVEY W. BENDER, B.S., DENTON A. COOLEY, M.D., *and* MICHAEL E. DE BAKEY, M.D.

A NUMBER of technics have been developed and used clinically to protect the brain and spinal cord from ischemic damage during aortic resection for aneurysm. The two methods which have been practical for this purpose were induced general body hypothermia and temporary vascular shunts.[2, 8, 9] Although these methods have been used successfully in a large number of thoracic aneurysms, certain disadvantages of each technic limit their usefulness significantly. For this reason recently we have employed temporary controlled extracorporeal circulation to by-pass the region of the aorta to be excised and to provide for arterial supply to the tissues and organs located distal to the occluding clamps.[3, 4] In general two methods of by-pass were used depending upon the location and extent of the aneurysm. For aneurysms of the descending thoracic aorta a simple extracorporeal circuit was used, removing blood proximally from the left atrium or aorta and delivering it distally through a pump into the abdominal aorta usually via the left common femoral artery. For aneurysms located in the ascending or transverse aortic arch cardiopulmonary by-pass using a pump oxygenator was necessary. With the latter method venous blood was removed from the vena cavae

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From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the Surgical Services of the Jefferson Davis Methodist and Veterans Administration Hospitals, Houston, Texas.

Supported in part by grants from the Houston Heart Association and the National Institutes of Health.

cut surface of the gross specimen All nine dogs subjected to experimental air embolism showed such vacuoles

Control dogs in which no air has been injected, when subjected to this procedure, will show a similar picture in about 10% of the cases This is probably due to inherent difficulties in taking the brain at autopsy



FIGURE 121 (Heimbecker)

Fourteen dogs were placed on the heart-lung machine, using the DeWall oxygenator Twelve of such dogs showed no air embolism The other two dogs showed positive results, a figure which is consistent with the error of the technic

This dog was perfused for half an hour at 50 cc /kilo of body weight (Figure 120) No air vacuoles are present

By contrast, here is the brain of a dog in which a small amount of air was accidentally trapped in the arterial line, and then seen to pass into the animal An air vacuole is present on the cut surface (Figure 121)

In conclusion, it would seem that this is a simple, direct method of demonstrating non-fatal gas embolism (with wide biological variations) in the gross specimen To resort to a microscopic search for air vacuoles in pathological sections would seem to be uncertain and even dangerous Within the limits of this technic, the DeWall oxygenator did not produce demonstrable air embolism

ure renal plasma flow (RPF) by methods previously described[6] Renal blood flow (RBF) was calculated from renal plasma flow with the hematocrit

Flow rates of the Sigmamotor or Mark pumps were carefully calibrated just prior to operation in each case In the aortic by



FIG 122 Comparison of average mean pressure in the aorta below the level of occlusion with the average pump flow rate To insure a functional pressure (above filtration level) it is necessary to pump at a rate of at least 20 cc per kg of body weight per minute In the average adult a flow rate of at least 1200 cc per minute is usually necessary

pass series the flow rates were low and somewhat variable in the first few patients but later approached 1,200 to 1 800 cc per minute This followed our appraisal that 20 cc per kg of body weight per minute probably represented the minimal flow rate for satisfactory perfusion pressure (Fig 122) It was customary to begin perfusion at about half such a calculated flow rate and gradually increase it making necessary adjustments from time to time to

pumped through a bubble diffusion oxygenator and returned through a femoral catheter

The purpose of this study was to estimate renal blood flow and glomerular filtration rate during extracorporeal circulation in a series of patients having resectional therapy of thoracic aortic aneurysms With these data coupled with direct manometric blood pressure determinations, it was possible to estimate the effectiveness of the perfusion blood flow in each case

METHODS

Two groups of patients were used in the study, one requiring aortic pump by-pass for aneurysms of the descending thoracic aorta, and the second, cardiopulmonary by-pass for aneurysms of the ascending thoracic aorta and cardiac operations In the former group, studies were performed on twenty-three patients in whom temporary extracorporeal circulation was used during resection of aneurysms of the descending thoracic aorta Following heparinization (1 mg per kg body weight) a perforated 3/16 inch polyvinyl tube was placed in the left atrium through the left atrial appendage A distal catheter was threaded proximally through an arteriotomy in one common femoral artery The two were then connected to a Sigmamotor finger pump or Mark roller pump

In the second group, consisting of eleven patients, cardiopulmonary by-pass was employed using a bubble diffusion oxygenator of the DeWall-Lillehei type Separate 3/16 inch polyvinyl caval catheters with inflow occlusion were employed Oxygenated blood was returned through a femoral catheter A third pump was utilized to perfuse the carotid arteries when resection necessitated occlusion of these vessels [3]

Mean blood pressure during the dependent period of aortic or cardiopulmonary by-pass was determined by direct measurement A mercury manometer was attached to plastic tubing leading to a 15-gauge needle inserted in the distal aorta All other mean blood pressures were derived from auscultatory pressures by adding one third of the pulse pressure to the diastolic pressure Inulin was used to measure glomerular filtration rate (GFR) and low concentrations (2-4 mg per cent) of para-aminohippurate to meas-

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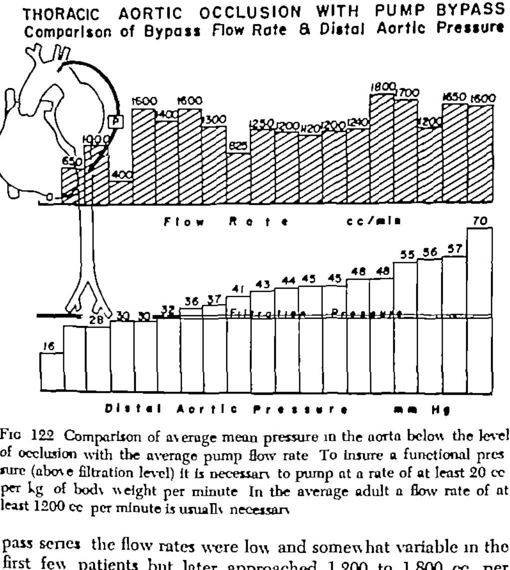


FIG 122 Comparison of average mean pressure in the aorta below the level of occlusion with the average pump flow rate To insure a functional pressure (above filtration level) it is necessary to pump at a rate of at least 20 cc per kg of body weight per minute In the average adult a flow rate of at least 1200 cc per minute is usually necessary

pass series the flow rates were low and somewhat variable in the first few patients but later approached 1,200 to 1 800 cc per minute This followed our appraisal that 20 cc per kg of body weight per minute probably represented the minimal flow rate for satisfactory perfusion pressure (Fig 122) It was customary to begin perfusion at about half such a calculated flow rate and gradually increase it making necessary adjustments from time to time to

make a proximal aortic pressure about 10 to 20 mm Hg above the preoperative blood pressure The flow rate for the pump oxygenator was 35 cc per kg of body weight per minute, except when operational factors forced a slight reduction

Records of the occlusion or dependent time and mean pump flow rates were made in each case Observations of blood pressure, renal blood flow, and glomerular filtration rate were made before operation, during anesthesia with thoracotomy, during the period of extracorporeal circulation, and following the re-establishment of normal circulation

RESULTS

Group 1, Aortic By-Pass. In Table I are assembled the observations on twenty-four patients having resection of aneurysms of the descending thoracic aorta with the pump by-pass The period of aortic cross-clamping ranged from 17 to 170 minutes The flow rates varied from 360 to 1,800 cc per minute and averaged 1,158 Mean blood pressure before operation averaged 103 mm Hg and was not significantly altered by anesthesia and thoracotomy When the distal aortic arch was occluded, the average mean blood pressure in the right arm rose to 114 mm Hg ranging, from 90 to 139 mm Hg Pressure in the distal aortic segment averaged 47 mm Hg and ranged from 28 to 70 mm Hg After the release of the clamps and discontinuance of the pump, the mean blood pressure was 102 mm Hg for the group

Renal blood flow and glomerular filtration rates generally correlated well with the blood pressure Anesthesia and thoracotomy had little effect on average renal blood flow, although glomerular filtration rate fell to 68 per cent of control During the period of circulatory support with the pump by-pass, the mean of renal blood flow fell to 8 per cent of controls and in glomerular filtration rate to 6 for this group In two patients having the lowest pressures in the distal aorta, 28 mm Hg, there was no measurable renal function In the patient with the highest distal aortic pressure, 70 mm Hg, renal blood flow was 124 cc per minute or 12 per cent of control In the patients with the lowest aortic pressures, the glomerular filtration rate was zero, and in the two patients with the highest pressures, the rate was 7 and 10 cc per

TABLE I

RENAL HEMODYNAMICS DURING AORTIC BY-PASS WITH A PUMP

No.	Pt.	Age	Race Sex	Occlusion Time (Min.)	Weight Kg.	Mean Pump Flow Rate (cc./min.)	Mean Blood Pressure (mm. Hg.) C	D₁	D₂ Up	D₂ Low	D₃	D₄	Renal Blood Flow (cc./min.) C	D₁	D₂	D₃	D₄	Glomerular Filtration Rate (cc./min.) C	D₁	D₂	D₃	D₄
1	R B	43	WM	[illegible]	[illegible]	825	[illegible]	—	—	—	—	85	1510	—	—	—	[illegible]	127	—	—	—	115
2	M L	44	WM	45	[illegible]	1200	99	84	106	44	84	93	1350	1494	30	1806	[illegible]	143	156	5	[illegible]	100
3	J	67	WF	35	47	650	93	60	110	28	—	89	500	—	—	—	370	62	—	—	—	43
4	J D	42	WM	57	61	960	106	87	100	—	—	95	1200		—	—	1097	79	—	—	—	107
5	S H	52	WM	45	[illegible]	400	87	—	—	—	—	92	635	—	—	—	387	95		—		72
6	O D	61	CM	45	82	825	123	120	120	41	116	93	917	18	29	1148	917	156	9	3	93	103
7	A H	45	WF	35	39	1300	107	127	124	37	112	—	759	587	11	1103	—	115	32	1	62	—
8	B A	62	WF	17	[illegible]	1200	88	102	92	43	100	—	600	452	393	258	—	63	19	11	10	—
9	B M	57	WM	70	57	400	110	100	112	38	87	104	899	407	[illegible]	210	—	91	31	[illegible]	23	31
10	E G	[illegible]	WM	48	74	1250	114	110	126	43	118	99	539	977	50	595	529	86	66	2	53	69
11	O C	64	WM	43	80	1210	110	118	130	48	—	119	318	869	32	—	823	19	17	2	—	71
12	D H	61	WF	27	65	1250	126	118	137	44	128	—	253	385	19	195	—	30	10	10	39	—
13	C S	47	WM	60	60	1000	120	105	125	29	80	—	1098	2795	[illegible]	2973		134	114	[illegible]	96	—
14	B H	57	WM	37	66	1375	130	105	132	69	—	112	819	4	6	[illegible]	317	89	5	4	−2	35
15	N M	[illegible]	CM	[illegible]	59	1700	93	80	105	[illegible]	—	—	757	851	7	356	—	86	29	3	16	—
16	A P	48	WM	170	[illegible]	1200	106	—	—	—	—	118	704	—	—	—	—	59				—
17	F C	49	WM	82	52	1000	103	77	102	40	100	87	825	800	1	—	712	87	65	3	—	85
18	M	65	WM	27	34	1120	89	90	103	43	105	90	620	—	—	—	578	74	—	—	—	61
19	L B	31	WM	81	65	1600	100	73	90	70		—	996	300	124	—	—	63	31	7	—	—
20	H	39	WM	2	74	1400	102	110	123	34	117	—	610	—	31	—	—	111	—	1	—	—
21	H B	61	WM	29	86	1800	103	94	115	48	88	—										
22	I B	35	CF	24	77	1050	95	90	115	27	105	—										
23	N B	[illegible]			75	1000	75	—	110	36	—	—										
Mean		55		41	68	1158	103	90	114	43	104	95	829	740	51	918	920	99	58	4	48	82
Per cent of Control								94	111	44	99	85		69	6	110	99		69	4	34	92
Mean Per cent of Control								84	111	45	98	94		91	8	101	104		69	4	40	90

Key to Abbreviations: C—Before operation
D₁—During thoracotomy before occlusion of the aorta.
D₂—During occlusion of the aorta.
D₃—During thoracotomy after occlusion of the aorta.
D₄—Following operation.

make a proximal aortic pressure about 10 to 20 mm Hg above the preoperative blood pressure The flow rate for the pump oxygenator was 35 cc per kg of body weight per minute, except when operational factors forced a slight reduction

Records of the occlusion or dependent time and mean pump flow rates were made in each case Observations of blood pressure, renal blood flow, and glomerular filtration rate were made before operation, during anesthesia with thoracotomy, during the period of extracorporeal circulation, and following the re-establishment of normal circulation

RESULTS

Group 1, Aortic By-Pass. In Table I are assembled the observations on twenty-four patients having resection of aneurysms of the descending thoracic aorta with the pump by-pass The period of aortic cross-clamping ranged from 17 to 170 minutes The flow rates varied from 360 to 1,800 cc per minute and averaged 1,158 Mean blood pressure before operation averaged 103 mm Hg and was not significantly altered by anesthesia and thoracotomy When the distal aortic arch was occluded, the average mean blood pressure in the right arm rose to 114 mm Hg ranging, from 90 to 139 mm Hg Pressure in the distal aortic segment averaged 47 mm Hg and ranged from 28 to 70 mm Hg After the release of the clamps and discontinuance of the pump, the mean blood pressure was 102 mm Hg for the group

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TABLE I

RENAL HEMODYNAMICS DURING AORTIC BY-PASS WITH A PUMP

No.	Pt.	Age	Race Sex	Occlusion Time (Minutes)	Weight Kg	Mean Pump Flow Rate (cc./min.)	Mean Blood Pressure (mm. Hg.) C	D	D₁ Up	D₁ Low	D	D	Renal Blood Flow (cc./min.) C	D	D	D	D	Glomerular Filtration Rate (cc./min.) C	D	D	D	D
1	R.B.	43	WM	30	62	825	89	—	—	—	—	89	1310				907	127				115
2	M.L.	44	WM	15	99	1200	95	84	100	44	81	95	1338	1161	30	1808	1888	111	198	3	89	140
3	J.S.	67	WF	35	47	650	93	80	110	68		88	500			—	370	62				65
4	J.B.	42	WM	37	61	300	104	87	100			95	1200			—	1097	79				103
5	S.H.	62	WM	15	80	400	97	—		—		92	657				387	98				72
6	O.B.	61	CM	15	82	925	123	129	120	41	118	93	917	18	28	1118	937	130	9	7	93	103
7	A.H.	13	WF	85	59	1500	107	127	124	37	112		741	897	11	1103		113	32	1	82	
8	D.A.	62	WF	17	63	1200	89	102	92	43	100	—	800	172	333	238		64	19	11	10	
9	D.M.	57	WM	70	87	400	110	108	112	30	87	101	899	107	0	210	—	91	31	0	24	31
10	J.G.	66	WM	40	78	1250	114	118	128	47	118	89	459	977	50	399	829	81	48	2	53	46
11	O.C.	64	WM	45	80	1410	110	118	138	49		119	319	665	32		623	49	47	2		71
12	D.H.	61	WF	27	67	1200	128	118	133	88	129		253	565	19	193		58	40	10	33	
13	C.S.	47	WM	60	80	1000	120	103	123	29	60	—	1098	2793	0	2073		131	114	0	98	
14	B.H.	57	WM	37	64	1375	130	103	132	69	—	112	619	6	8	0	517	69	9	1	−2	53
15	N.M.	50	CM	85	58	1700	83	80	103	45	—		737	641	7	518	—	88	29	3	16	
16	A.P.	48	WM	170	60	1600	106	—	—	—	—	110	701			—		59				
17	T.C.	49	WM	62	52	1600	103	77	108	30	100	87	925	680	1	—	712	87	69	3		85
18	S.M.	65	WM	27	51	1120	89	80	103	43	103	99	619				374	71		—		81
19	J.B.	61	WM	61	65	1600	100	73	98	70		—	898	380	121			65	31	7		—
20	H.	69	WM	72	74	1400	102	110	123	32	117	—	619		31	—		111	—	1		—
21	H.D.	61	WM	29	84	1800	103	88	113	43	93	—										
22	L.B.	73	CT	24	77	1050	93	90	113	57	103	—										
23	S.D.	53			75	1000	74	—	116	34	—	—										
Mean		53		41	69	1148	101	89	114	43	102	98	849	710	33	913	828	99	50	4	49	82
Per cent of Control								90	111	44	99	95		89	6	110	99		67	4	51	92
Mean Per cent of Control								91	111	43	98	94		81	8	101	104		64	6	58	90

Key to Abbreviations C—Before operation.
D—During thoracotomy before occlusion of the aorta.
D₁—During occlusion of the aorta.
D₂—During thoracotomy after occlusion of the aorta.
D₃—Following operation.

TABLE II

RENAL HEMODYNAMICS DURING CARDIOPULMONARY BY-PASS WITH A PUMP OXYGENATOR

No	Patient	Age	Race Sex	Dependent Time (Minutes)	Mean Pump Flow Rate (cc/min)	Mean Blood Pressure (mm Hg)					Renal Blood Flow (cc/min)					Glomerular Filtration Rate (cc/min)				
						C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1	I A	14	WM	12	1250	67	73	—	75	72	530	226	165	44	291	64	28	21	4	45
2	B G	13	WF	8	1300	92	94	—	108	80	573	404	0	805	496	68	44	0	61	63
3	W H	50	WM	31	2500	83	—	—	—	83	1076	—	—	—	821	102	—	—	—	115
4	L H	42	WI	7	2170	70	92	35	88	88	421	404	58	477	426	57	60	9	43	65
5	M H	42	WI	30	2135	93	94	—	34	76	873	676	117	83	277	77	84	14	14	23
6	I I	27	CF	9	1600	75	65	—	67	—	517	432	—	219	—	59	56	—	28	—
7	P J	11	WF	15	1000	97	83	—	82	75	510	375	309	200	337	45	43	39	21	41
8	M M	49	CM	45	2200	103	103	50	120	—	570	511	33	191	—	151	66	5	17	—
9	B M	56	WM	45	1650	96	77	52	89	—	876	137	102	873	—	99	14	33	51	—
10	F P	27	WI	22	1650	71	88	37	62	—	842	610	185	344	—	61	69	19	36	—
11	J S	11	WI	6	1100	86	129	—	88	98	600	424	138	464	527	67	57	22	51	79
Mean		31		21	1687	85	90	44	81	82	672	420	156	370	454	77	52	19	33	62
Per cent of Control							106	52	95	96		63	23	55	68		68	25	43	81
Mean Per cent of Control							107	51	97	99		69	24	60	72		77	29	48	90

Key to Abbreviations C—Before operation
D_1—During thoracotomy before cardiopulmonary by-pass
D_2—During cardiopulmonary by-pass
D_3—During thoracotomy after cardiopulmonary by-pass
D_4—Following operation

minute respectively Immediately after release of the occluding clamps renal blood flow generally returned to normal but glomerular filtration remained somewhat depressed This function however returned toward normal during the later postoperative period.

Group 2, Cardiopulmonary By pass The data derived from studies on patients having cardiopulmonary by pass with the pump-oxygenator are presented in Table II With this procedure there is no proximal and distal pressure differential since the entire body is perfused The mean pressure in the aorta during by pass averaged 44 mm Hg and ranged from 35 to 52 mm Hg Hence measurable renal function was generally greater than that found with aortic pump by pass Renal blood flow averaged 24 per cent of control and glomerular filtration rate 29 per cent After resumption of normal circulation renal blood flow and glomerular

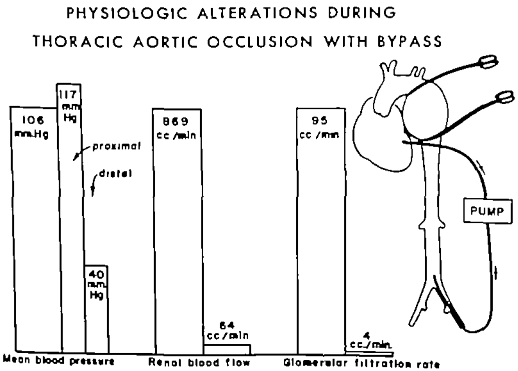


FIG 123 Mean blood pressure renal blood flow and glomerular filtration rate during aortic by pass with a pump Mean blood pressure in the proximal aorta rose an average of only 11 mm Hg and was sustained at a level of 40 mm Hg in the distal aorta. Though renal function was greatly reduced, it was sufficient to allow filtration and prevent ischemic damage

TABLE II

RENAL HEMODYNAMICS DURING CARDIOPULMONARY BY-PASS WITH A PUMP OXYGENATOR

No	Patient	Age	Race Sex	Dependent Time (Minutes)	Mean Pump Flow Rate (cc/min)	Mean Blood Pressure (mm Hg)					Renal Blood Flow (cc/min)					Glomerular Filtration Rate (cc/min)				
						C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
1	J A	14	WM	12	1250	67	73	—	75	72	530	226	165	44	291	64	28	21	4	45
2	B G	13	WF	8	1300	92	94	—	108	80	573	404	0	805	496	68	44	0	61	63
3	W H	30	WM	31	2500	83	—	—	—	83	1076	—	—	—	821	102	—	—	—	115
4	L H	42	WF	7	2170	70	92	35	88	88	421	404	58	477	426	57	60	9	43	65
5	M H	42	WF	30	2135	93	94	—	34	76	873	676	117	83	277	77	84	14	14	23
6	L I	27	CF	9	1600	75	65	—	67	—	517	432	—	219	—	59	56	—	28	—
7	P I	11	WF	15	1000	97	83	—	82	75	510	375	309	200	337	45	43	39	21	41
8	M M	49	CM	45	2200	103	103	50	120	—	570	511	33	191	—	151	66	5	17	—
9	B M	56	WM	45	1650	96	77	52	89	—	876	137	402	873	—	99	14	31	51	—
10	L P	27	WF	22	1650	71	88	37	62	—	842	610	185	344	—	61	69	19	36	—
11	J S	11	WF	6	1100	86	129	—	88	98	600	424	138	464	527	67	57	22	51	79
Mean		31		21	1687	85	90	44	81	82	672	420	156	370	454	77	52	19	33	62
Per cent of Control							106	52	95	96		63	23	55	68		68	25	43	81
Mean Per cent of Control							107	51	97	99		69	24	60	72		77	29	48	90

Key to Abbreviations C—Before operation
D_1—During thoracotomy before cardiopulmonary by-pass
D_2—During cardiopulmonary by-pass
D_3—During thoracotomy after cardiopulmonary by-pass
D_4—Following operation

shown that without any type of by pass collateral circulation will produce a blood pressure below the point of aortic occlusion of 12 to 30 mm Hg (Fig 124) Hence the pump by pass probably adds little protection from ischemic damage to distal vascular beds if the flow rate is insufficient to produce a distal pressure greater than filtration pressure or about 32 mm Hg That the technics used were at least qualitatively accurate at these low pressure levels was demonstrated by one case not included in the tables In this patient one renal artery was perfused as well as the distal aortic segment during resection of a thoracoabdominal aneurysm Under these conditions the calibrated renal perfusion rate closely approximated the measurable renal blood flow When the renal perfusion rate of 70 cc per minute was decreased to 50 cc per minute the measurable renal blood flow with this clearance tech nic fell from 53 cc per minute to zero Thus at least in this kidney the critical flow rate for filtration was between 50 and 70 cc per minute

Group 2 Cardiopulmonary By pass In the case of cardiopul

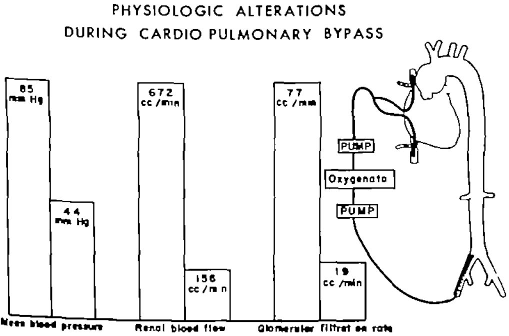


FIG 125 During cardiopulmonary by pass with a pump oxygenator at a flow rate approaching 35 cc per kg body weight per minute the mean blood pressure was 44 mm. Hg This pressure sustained significant renal blood flow and glomerular filtration

filtration rate returned to 72 per cent and 80 per cent of control values respectively

DISCUSSION

Group 1, Aortic By-pass. This study indicates the minimal flow rates which should be used during resectional procedures for aneurysms of the descending thoracic aorta Flow rates less than 20 cc per kg of body weight per minute frequently were not sufficient to produce a lower aortic blood pressure above the filtration level, or about 32 mm Hg (Fig 122) To obtain a functional pressure in the distal aortic segment, it is necessary to perfuse at a rate of at least 20 cc per kg of body weight per minute The average distal aortic pressure during pump by-pass for the group was only 40 mm Hg, however, even this low pressure level was sufficient to produce measurable renal blood flow (Fig 123) When distal aortic pressure fell below the filtration level, no measurable function was observed Previous studies[7, 8] have

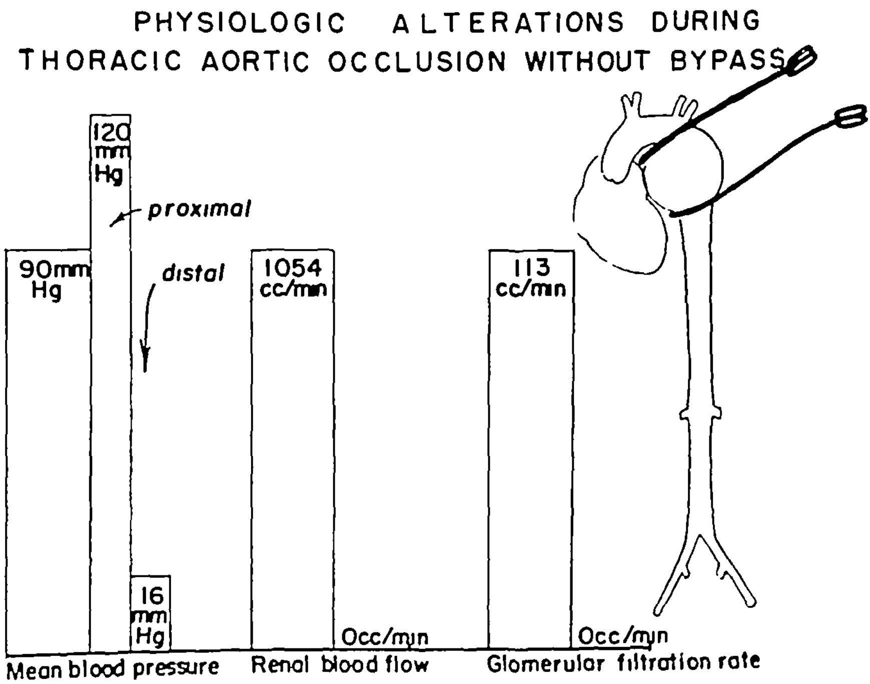


FIG 124 Occlusion of the descending thoracic aorta as illustrated in this case produced a rise in mean blood pressure in the arm of 30 mm Hg The pressure in the aorta below the occluding clamps fell to 16 mm Hg, far below the filtration level necessary for renal function

aorta in fusiform aneurysm using cardiac by pass *J.A.M.A* *162* 1158 1956
5 DeBakey M E Creech O and Morris G C Aneurysm of thoracoabdominal aorta involving the celiac, superior mesenteric, and renal arteries Report of four cases treated by resection and homograft replacement *Ann Surg* *144* 459 1956
6 Handley C A Sigafoos R and LaForge M Proportional changes in renal tubular reabsorption of dextrose and excretion of P aminohippurate with changes in glomerular filtration *Am J Physiol* *159* 175 1949
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8 Moyer J H., Heider C F., Morris G C., and Handley C A. Renal failure I The effect of complete renal artery occlusion for variable periods of time as compared to exposure to sub-filtration arterial pressures below 30 mm Hg for similar periods *Ann Surg* *145* 41 1957
9 Moyer J H., Heider C F., Morris G C and Handley C A. Hypothermia III The effect of hypothermia on renal damage resulting from ischemia. *Ann Surg* *146* 145 1957

monary by-pass with the pump oxygenator, this study again demonstrates that a flow rate of 35 cc per kg of body weight per minute supports a mean blood pressure ranging from 35 to 60 mm Hg This represents a mean pressure of 51 per cent of the preoperative level In spite of an almost fourfold increase in the calculated renal vascular resistance, renal blood flow was maintained at 24 per cent of control values (Fig 125) Hence, as previously demonstrated, renal circulation must remain sufficient to prevent ischemic damage [1]

SUMMARY

Controlled extracorporeal circulation with a pump for aortic by-pass has been employed during the resectional therapy of aneurysms located in the descending thoracic aorta Studies of blood pressure, renal blood flow, and glomerular filtration rate were performed during these procedures. These observations indicate that a pump flow rate of at least 20 cc per kg of body weight per minute is necessary to provide an aortic blood pressure distally which permits measurable renal function during the by-pass

Controlled extracorporeal circulation with a pump-oxygenator for cardiopulmonary by-pass has been employed during the resection and replacement of aneurysms located in the ascending and transverse aortic arch Similar studies performed in these patients indicate that a perfusion rate of 35 cc per kg of body weight per minute is sufficient to support renal function during by-pass and prevent ischemic damage to the kidney

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3 Cooley, D A, DeBakey, M E, and Morris, G C Controlled extracorporeal circulation in surgical treatment of aortic aneurysms *Ann Surg*, *146* 473, 1957

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THE EFFECTS OF TOTAL BODY PERFUSION UPON THE LUNGS

By

F D DODRILL, M.D

ONE OF the most serious difficulties encountered in total body perfusion is the profound effect upon the lungs that may occur to certain patients undergoing perfusion It is indeed discouraging to perform open cardiac corrective surgery to have the patient remain in excellent condition throughout the procedure and for a day or two thereafter finally succumbing to pulmonary insufficiency while the heart itself remains strong to the very end This disease which I shall discuss has been referred to as atelectasis of the lung as we have heretofore known. The condition might more properly be called pulmonary or alveolar collapse This does not of course occur in all cases but one cannot predict in which patient it will occur

It is not often seen in short periods of perfusion such as four to five minutes The longer the duration of the perfusion the more likely the complication is to occur

The first sign of the complication is the increased respiratory rate which is present in those patients who have the complication almost immediately after the operation is finished

The typical course of the disease is as follows immediately after the conclusion of the operation the respiratory rate of the patient is increased It is often 40 to 50 per minute There may be slight cyanosis The condition may become progressively worse and death usually occurs on the second or third day although the lives of some patients may be prolonged for six to seven days There are often signs of increasing pulmonary insufficiency as time goes on The heart and blood pressure remains good until the very end It is primarily a pulmonary death With less severe injuries the patient gradually recovers

DISCUSSION

DR ELTON WATKINS, Boston The excellent material on renal function just presented by Doctor Morris seems to me to bear upon an important aspect of flow during heart-lung by-pass It is well-known that the kidneys are the most sensitive organs in the body in their manner of response to slight degrees of vasoconstriction They are the first organs to cease functioning when minor circulatory stress is inflicted Consequently, if we can maintain some semblance of renal function during heart-lung by-pass, we can be sure that the brain and other organs are receiving adequate blood supply

Mr Robert Replogle, working in our laboratory, has developed methods for the rapid serial measurement of effective renal blood flow by observation of the clearance of I^{131}-Diodrast Numerous determinations may be made during the course of a by-pass We have been concerned to find that effective renal blood flow ceases within five minutes after the start of a dog by-pass at a high perfusion rate of 1 8 liters/minute/square meter body surface area (about 60-80 ml /min/Kg body weight) This striking change occurs despite minimal acid-base changes and an adequate arterial pressure Renal suppression continues through forty-five to sixty minutes by-pass and persists for sixty to one hundred twenty minutes after by-pass Renal flow returns without rebound No escape has been observed during the period of by-pass Body oxygen consumption has reached a plateau at perfusion rates considerably below the 1 8 liter per square meter value In control sham operations, where cannulae have been inserted but no by-pass carried out, effective renal blood flow drops to only about 75 per cent of the control post-induction value We believe that the disparity between the latter control value and the by-pass value represents an indication of renal suppression due most probably to vasoconstriction as a result of inadequate flow It seems significant that this change is occurring despite minimal evidence of tissue ischemia (minimal acid-base change) and the absence of arterial hypotension In our quest for the "ideal" perfusion rate, such studies of organ function must be carried out and interpretations balanced against the evils of increased blood trauma created by high perfusion rates Kidney function studies seem paramount to us because of their low threshold of sensitivity to circulatory stress

hypertension While it must be admitted that pulmonary collapse may be more common in patients with high pulmonary resistance there are some serious doubts as to it being the primary etiological agent This is true because pulmonary or alveolar collapse may occur postoperatively in patients who do not have increased pulmonary pressure or increased resistance Moreover, we have had for many years a similar condition in the disease of patent ductus arteriosus which is a similar physiological shunt resulting sometimes in increased pulmonary artery pressure All of us have had a number of these cases over the years in which the ductus was eliminated without any evidence whatsoever of pulmonary collapse postoperatively This statement does not however include ducti with reversal of shunt. 5 Increased oxygen tension of the blood. It has recently been reported by Penido Swan and Kirklin of the Mayo Clinic [1] using the bubble oxygenator that the tension of the oxygen of the blood may be vastly increased beyond normal This occurs when the saturation of the blood is increased beyond the 100 per cent level If this is the cause of the condition under discussion then those who use other types of oxygenators such as the screen or the membrane type should not encounter this condition to any significant degree 6 Minute emboli could account for this erratic type of pulmonary collapse However prolonged examination of large numbers of microscopic sections have failed to reveal any microscopic evidence

One additional point should be kept in mind It is well known that patients with one congenital condition are more apt to have other congenital defects May it not be possible that some intricate abnormality of the lung may be present in these cases which is not present in normal people?

In addition to all these factors mentioned it is probable that any serious abnormality in the chemical structure of the blood may be an etiological agent

Regardless of what may be the etiology of this condition the fact remains inescapable that in certain patients during the course of total body perfusion there is an injury to the pulmonary alveolus This is more in the nature of a physio-pathological rather than a demonstrable pathological defect

INCIDENCE

The incidence of this complication varies from clinic to clinic but I suspect that the real incidence is much larger than we have been led to believe In my own experience, this has been the main and predominating complication I think it is fair to state that country-wide the incidence of pulmonary collapse may be as high as 15 to 25 per cent Fortunately, it is occurring less frequently as time goes on and as more ideal perfusions are performed

Various theories have been put forth to explain this condition One might consider the following factors 1 Bilateral thoracotomy Some have thought that since bilateral thoracotomy is done in these patients, in order to expose the heart, that the coughing mechanism is ineffectual postoperatively and that the patient cannot evacuate his secretions However, many bilateral thoracotomies have been performed for other conditions and this pulmonary collapse has not, to my knowledge, ever been encountered in cases undergoing bilateral thoracotomy for other conditions 2 Right ventriculotomy Since most of the patients undergoing open cardiac surgery during perfusion have a right ventriculotomy in order to expose the septum, it has been considered by some that the right ventricle has failed in the postoperative period, thereby producing the pulmonary condition Inasmuch as the pathology of this condition under discussion is not one of pulmonary stasis or congestion and since there are no other signs of right ventricular failure, it is difficult to see how this is an important factor Moreover, the heart remains strong and the patient dies essentially of pulmonary insufficiency 3 Anoxia and retention of carbon dioxide in the alveolar tissues Since the lungs are bypassed except for whatever collateral circulation there may be present between the bronchial artery supply and the alveoli, both anoxia and carbon dioxide retention have been presumed to be present and have been incriminated as the etiological agent To my knowledge, no concrete evidence has been presented to substantiate this viewpoint 4 Increased pulmonary resistance With many patients undergoing perfusion and open cardiac surgery, there is increased pulmonary artery pressure and, in some cases increased pulmonary resistance, due to the arteriolar hypertrophy which may eventually occur in patients with long-standing pulmonary

hypertension While it must be admitted that pulmonary collapse may be more common in patients with high pulmonary resistance there are some serious doubts as to it being the primary etiological agent This is true because pulmonary or alveolar collapse may occur postoperatively in patients who do not have increased pulmonary pressure or increased resistance Moreover we have had for many years a similar condition in the disease of patent ductus arteriosus which is a similar physiological shunt resulting sometimes in increased pulmonary artery pressure All of us have had a number of these cases over the years in which the ductus was eliminated without any evidence whatsoever of pulmonary collapse postoperatively This statement does not however include ducti with reversal of shunt 5 Increased oxygen tension of the blood It has recently been reported by Penido Swan and Kirklin of the Mayo Clinic [1] using the bubble oxygenator that the tension of the oxygen of the blood may be vastly increased beyond normal This occurs when the saturation of the blood is increased beyond the 100 per cent level If this is the cause of the condition under discussion then those who use other types of oxygenators such as the screen or the membrane type should not encounter this condition to any significant degree 6 Minute emboli could account for this erratic type of pulmonary collapse However prolonged examination of large numbers of microscopic sections have failed to reveal any microscopic evidence

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FIG 126 Roentgen examination of the chest showing only minor areas of collapse

One of the striking features of this pulmonary collapse is the fact that the Roentgen examination of the lungs does not show serious pulmonary disease (Figure 126) This film was taken on the



Fig 127 Section of lung showing areas of collapse

fourth postoperative day The lungs are fully expanded, there is no pulmonary fluid and there is no evidence of consolidation or atelectasis in the usual term However, this patient was in serious pulmonary insufficiency at the time this Roentgenogram was taken and died a few hours afterwards

PATHOLOGY

This type of pulmonary collapse is peculiar in that it has no segmental distribution It is, therefore, totally unlike ordinary

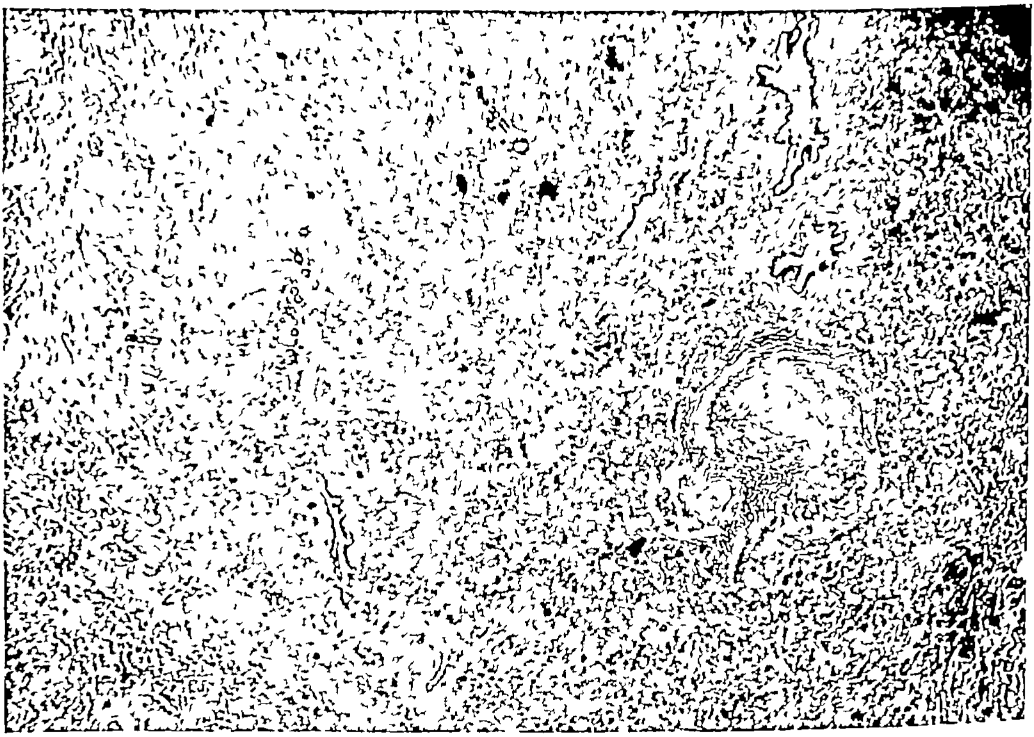


FIG 128 Microscopic section of the collapsed lung

postoperative atelectasis of the lung The condition is characterized by areas of collapse surrounded by aerated lung as illustrated in Figure 127 The microscopic examination of the collapsed alveoli reveals no abnormal cellular changes save for one which I shall presently mention, Figure 128 There is no evidence of cellular infiltration and no evidence of pulmonary edema A histologic change which may be of some significance is the fact that the elastic fibers of the alveoli are distorted, fragmented and thickened, Figure 129 This would seem to be the only concrete micro-



FIG 129 Elastic tissue stain of collapsed lung demonstrating distortion and fragmentation of elastic tissue fibers

scopic change in cell structure Whether this is a cause or an effect is not known

TREATMENT

As in any case, the most effective treatment is the prevention Perfusion should take place under the most ideal circumstances The blood should be arterialized in as near normal condition as is possible A careful chemical balance is imperative Tracheotomy is indicated early in the postoperative period or at any time when it is thought that the tracheobronchial tree can be kept more free of any possible secretions Mechanical respiration is indicated in the serious injuries of the lung The obstruction of the bronchial artery supply during the by-pass may be helpful This can be accomplished by applying a tourniquet around the hilus of the lung Some patients with congenital heart disease have a greatly increased bronchial artery system and the blood flow may be great during the by-pass

In patients with this serious complication, a tracheotomy is strongly indicated Bronchoscopy may be especially effective, since if the aspirating tip is inserted into the bronchial orifices, secretions often are obtained although none are seen In tracheotomized patients, bronchoscopy may be repeated as often as necessary The complication can be eliminated only by performing more perfect perfusions

In addition to alveolar collapse, there may be the usual type of atelectasis which responds to the usual treatment such as coughing, tracheal suction or bronchoscopy

SUMMARY

The deleterious effects upon the lungs which may be produced by body perfusion consist in alveolar collapse This does not have a segmental distribution and is not atelectasis as we have heretofore known The fact is inescapable that an injury to the pulmonary alveolar membrane has been produced The only microscopic abnormality, aside from the collapse itself, is the apparent change in the elastic tissue fibers With more ideal perfusions the complication should largely disappear

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PULMONARY PARENCHYMAL CHANGES ASSOCIATED WITH CARDIO-PULMONARY BY-PASS

By

WILLIAM H. MULLER, JR., M.D., JAMES B. LITTLEFIELD, M.D.* *and* J. FRANCES DAMMANN, JR., M.D. (F.A.C.C.)

AMONG the most important and most frequent clinical complications associated with cardiopulmonary by-pass and open heart surgery are those related to the lungs. The increasing use of the heart-lung apparatus for open heart surgery has necessitated a better understanding of hemodynamic alterations occurring in the lung. These changes may be seen in a variety of forms, some of which are transient and of no great clinical significance, however, they may also appear in progressively more severe forms which may be irreversible and incompatible with life. Perhaps the most serious change is pulmonary hemorrhage which, in some instances, may be irreversible and it is with this change, which may occur in special circumstances, that this report is primarily concerned.

Anatomical Considerations: The circulation to the lungs is of dual origin. Anatomical emphasis has long been placed on the pulmonary arterial and venous vascular bed. The bronchial arteries are of great importance as collateral circulation because of their systemic arterial origin. Their intrapulmonary distribution has been thoroughly studied.[1, 2, 3] Miller,[2, 4, 5] in a number of reports, has demonstrated that systemic blood is returned from the bronchial artery system through two routes. Anastomoses between the pulmonary and bronchial arteries return a portion

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through the pulmonary veins while the remaining blood is re turned through the bronchial veins which enter the systemic venous circulation through a variety of points including most frequently the azygos or the hemiazygos or one of the intercostal veins Considerable controversy has arisen previously regarding the position of the anastomotic channels between the bronchial and pulmonary circulation Precapillary anastomoses have been definitely demonstrated by a number of investigators[6] however and the presence of capillary communications has long been known.

The function of the bronchial artery circulation has not been entirely understood It is known however that under some cir cumstances such as in certain types of congenital heart disease and some inflammatory or other pathologic processes the bronch ial arterial system does assume the major role of collateral cir culation[7,8,9] Its role as an avenue of collateral circulation in certain types of heart disease acquires greater clinical significance when the effect on the lung of total cardiopulmonary by pass is considered

Clinical Considerations During the past two years we have observed four patients who developed pulmonary edema with gross hemorrhage into the parenchyma either during cardiopul monary by pass or shortly after it was discontinued Two of these patients had transposition of the aorta and pulmonary artery with an interatrial septal defect One had a septum primum defect with a large left to-right shunt and high pulmonary artery pres sure the fourth had a ventricular septal defect with equal pres sure in the pulmonary and systemic arteries Speculation as to what might be the origin of this pulmonary damage including a review of the technical aspects of the procedures employed seemed to offer plausible reasons as to why pulmonary hemor rhage occurred.

First, during perfusion or shortly thereafter the pulmonary artery pressure must have risen sufficiently to cause rupture into the alveoli This pressure was presumed to have mediated through bronchial artery anastomoses into the pulmonary vascular bed It began to increase probably because the pulmonary artery had been occluded simultaneously with the aorta when potassium

citrate was administered to produce cardiac arrest In addition, it seemed logical that this pressure rose further when the defect between the right and left side of the heart was closed It also seemed plausible that upon the resumption of cardiac action, the difference in resistance to ventricular contractions created by the relatively high systemic arterial pressure which the pump oxygenator maintained might be considered to influence the development of pulmonary hemorrhage Under these circumstances, it is conceivable that right ventricular contractions become effective before those of the left ventricle, evolving a physiologic hemodynamic alteration not unlike transient left heart failure

In other patients, it has been noticed that the amount of blood returning to the heart through the pulmonary veins when cardioplegia is employed sems to be directly proportional to the degree of pulmonary hypertension It is well known that changes of luminal narrowing due to intimal fibrosis and medial hypertrophy occur in the presence of long-standing pulmonary hypertension associated with congenital heart disease and a left-to-right shunt This, in essence, is not physiologically unlike changes which occur with the tetralogy of Fallot The anatomical difference is that the position of the pulmonary stenosis is in the small muscular pulmonary arteries instead of in the pulmonary valve or outflow tract to the right ventricle The obstruction to the flow of blood through the pulmonary circulation stimulates the development of the collateral bronchial artery circulation and a much higher bronchial artery blood flow into the pulmonary circulation occurs

Experimental Procedure. In an effort to determine the etiology of pulmonary hemorrhage, an investigative program was initiated in the research laboratory It was noted in early experiments that a dilated left auricle often accompanied bleeding into the lung The source of this blood was thought to be collateral circulation through the bronchial arteries rupturing through the pulmonary vascular bed into the alveoli In order to validate this assumption, the following experiment was performed

High bronchial artery blood flow was developed in one group of dogs by ligating the left pulmonary artery several months prior to the experiment Another group of normal dogs were used for control A right thoracotomy was employed The animals were

heparinized and the venae cavae were cannulated through the right auricular appendage and the azygos vein was ligated The femoral artery was cannulated and these cannulae were connected to the Clark pump oxygenator Systemic flow rates 54 to 85 cc per kilogram per minute were used The aorta and pulmonary artery were clamped and cardioplegia was induced with potassium citrate A right cardiotomy was performed. The systemic arterial pulmonary arterial and left auricular pressures were continuously recorded and serial lung biopsies were obtained The pulmonary circulation was isolated in both groups and the only blood entering the lungs was via the bronchial arteries This blood could not pass through the occluded pulmonary artery and therefore entered the left atrium Since the auricular and ventricular septa were intact, its only recourse was to escape into the left ventricle and through the coronary arteries or to become pooled in the pulmonary vascular bed

A standard occlusion time of thirty minutes was used and 30 mm of mercury was selected as the pulmonary edema level During this time the pulmonary artery pressure in the animals with normal bronchial artery blood flow did not rise above this level In the animals with a physiologic pneumonectomy and high bronchial artery blood flow the pressure rose to levels of 35 to 82 mm of mercury and concomitantly the femoral artery blood pressure fell In this group gross and microscopic pulmonary hemorrhage occurred ten to thirty minutes after clamping the aorta and pulmonary artery This did not occur in the animals with normal bronchial artery flow When the clamp was removed from the pulmonary artery in the animals with high bronchial artery blood flow permitting decompression through a right ventriculotomy the pressure became normal in the pulmonary artery and left atrium After the clamp had been removed from the aorta and the heart allowed to resume contractions a rise in pulmonary artery pressure reaching from 30 to 50 mm occurred in the animals with high bronchial blood flow There was usually only a slight rise in the controlled group

Conclusions These experiments clearly demonstrate the influence of the bronchial artery circulation in raising the pulmonary artery pressure and producing pulmonary hemorrhage when out

flow in both directions is occluded It also demonstrates the probability that if one relates these data to patients, those patients having a high collateral bronchial artery blood flow may be more apt to develop pulmonary parenchymal damage than those with more normal bronchial arteries The former group includes patients with cyanotic heart disease, such as the tetralogy of Fallot and transposition of the aorta and pulmonary artery, and also those without cyanosis but with a high pulmonary pressure frequently associated with a large ventricular septal defect, and in older patients with large interatrial septal defects

We have concluded from this study that every effort should be made to maintain a low pulmonary artery pressure during total by-pass To accomplish this, the pulmonary artery should not be occluded The left auricle should be decompressed when the heart is slow to begin effective contractions and if one suspects pulmonary vascular changes of marked luminal narrowing which results in a high pressure and resistance, and which retards backflow through the pulmonary vascular bed Closure of the cardiotomy should be delayed until effective left ventricular contractions are present Although the occasion should seldom arise, excessive systemic blood pressures should not be allowed to develop which might, in turn, cause excessive bronchial artery blood flow

Since employing these general principles, hemorrhage into the pulmonary parenchyma has not been encountered in any patients who have undergone open heart surgery This includes those with both ventricular and complex atrial septal defects It appears that the time required for total by-pass may bear some relation to survival of the patient Aside from other factors, those with high collateral pulmonary circulation undergoing long operations might be more apt to develop pulmonary parenchymal damage whereas a shorter period of by-pass might be better tolerated

One should also take into consideration the amount of blood temporarily lost into the pulmonary vascular bed during cardiac arrest This might be manifested by a gradual drop in systemic pressure after the heart is stopped and one should correct this deficit by the addition of blood to the pumping system With resumption of heart action, care should be taken not to overload the circulation especially in the patient who has a preoperative

blood volume above normal associated with an intracardiac shunt which is corrected by the operation

During cardiac standstill it is preferable for the lungs to remain relatively motionless If respiration is continued at a normal rate either manually or with a mechanical respirator pressure changes are produced which serve to increase the bronchial to pulmonary artery collateral blood flow A satisfactory procedure to prevent this occurrence is to partially fill the lungs with a gas such as nitrous oxide and gently inflate and deflate at intervals of several minutes This aids in preventing atelectasis and does not significantly increase collateral blood flow

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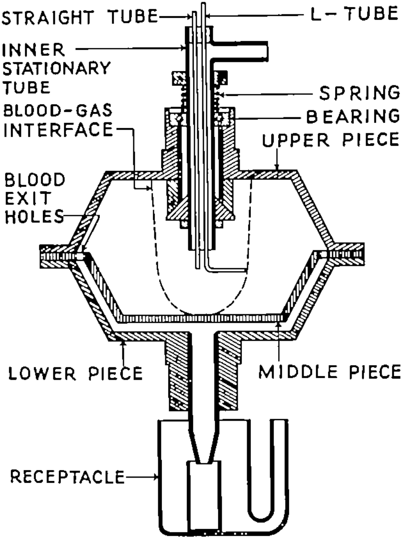


FIGURE 130 (Kusserow)

DR. BERT KUSSEROW New Haven I would like very briefly to invite the attention of the group to a defoaming apparatus or bubble separator depending solely upon physical forces for its action (Fig 130) With such a defoaming apparatus no foreign chemical substances are necessary to debubble blood. The device consists of a constant delivery low speed centrifuge The tremendous difference in the densities of blood and the respiratory gases makes it possible to effect separation of the latter with centrifugal forces of relatively low magnitude Hence only small speeds of rotation are needed Such a device would, of course also separate from the blood any fibrin clots or other particulate matter that might be present in it With careful design and construc-

DISCUSSIONS

DR L C CLARK, Yellow Springs I would like to make three points which I believe may help explain some of the discrepancies regarding oxygen poisoning and oxygen embolism regardless of what type of machine is used

First, it would be better if it were always made clear whether it was oxygen content or oxygen tension being referred to Plasma will dissolve more oxygen when equilibrated cold than when warm, though the tension is the same When this cold plasma is warmed it will increase in tension in a closed container but in an open container it will give off oxygen to maintain its equilibration with the surrounding medium The temperature shift of the dissociation curve of whole blood would add considerably to this increased oxygen content of the plasmas as the blood is warmed Oxygen embolism, but probably not oxygen poisoning, is possible if cool oxygen-saturated plasma is perfused into a warmer patient One way to prevent this occurrence is to keep patient and machine at the same temperature, another is to keep the oxygen content below full saturation by equilibration in a chamber under reduced pressure, and another is to control the oxygen content by some other means while monitoring the tension

The second point is that in the apparatus described in my paper this morning, oxygenation occurs at slightly reduced pressures so that the oxygen content is below full saturation, as revealed by oxygen tension measurement Lastly, there has been some conversation about producing gas embolism by the decompression resulting when arterial blood leaves the high-pressure line of the machine, through a constricted cannula, into the lower pressure arteries of the patient When a liquid containing a given gas tension is compressed, the gas tension in that liquid does not change unless and until the liquid itself is compressed, pressures far beyond those we are concerned with would be necessary

CHAIRMAN (DR MORROW) Dr Clark, do you think that, from a safety standpoint, it is important for all oxygenators to be equipped with an oxygen-tension electrode?

DR CLARK Yes, I believe this is wise and I think that it is easy enough to do and may become enough simpler in the future to represent no significant complication I know that everyone who has done this has learned much about the oxygenating characteristics of his machine as well as the oxygenation of the patient

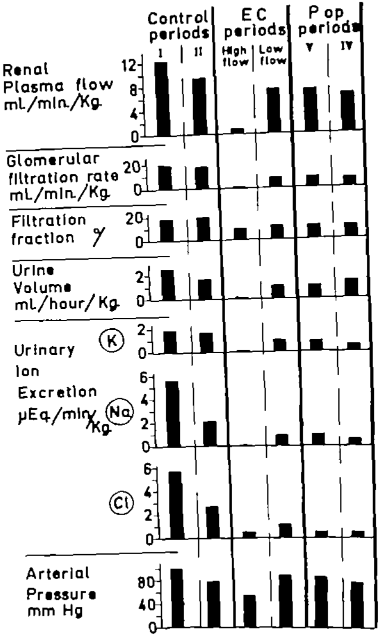


FIGURE 131 (Andersen) There is an error in labeling here The "High flow" and the "Low flow" labels should be exchanged

represents roughly a 25% reduction of the usual basal cardiac output of a dog

DR FRANCIS D MOORE, Boston Mass This acidosis is properly referred to as metabolic acidosis but it is helpful in addition to refer to it as "hypoxic acidosis" It is an acidosis arising from the release into

tion it is possible to reduce the traumatic effect upon the blood elements to a safe minimum The cross-sectional diagram of the defoamer illustrates its construction and operation The mixture of blood and bubbles drops to the center of the middle piece via the inner stationary tube, the latter being the only non-rotating component Here centrifugal force separates gaseous and liquid phases Slight positive pressure forces the defoamed blood into the receptacle below via the peripheral blood exit holes and the narrow interval between middle and lower pieces

DR MURRAY N ANDERSEN, Buffalo I would like to present some experimental studies of renal function performed at the Karolinska Institute with Doctor Senning We measured renal functions before, during, and after one-hour periods of extracorporeal circulation using the Crafoord-Senning pump-oxygenator Results are illustrated in this slide

There is an error in the slide and during the period of EC the high-flow and low-flow labels should be exchanged, Figure 131

The first control period was after anesthetization and gives control values for renal plasma flow, glomerular filtration rate, filtration fraction, urine excretion, and electrolyte excretion The second control period is after completion of thoracotomy and shows a slight decrease in all functions

During the high-low period, in which the flow rate was approximately 100 ml /Kg /min , all measurements remained at nearly control levels

During the low-flow period, with flow rates of approximately 40 ml /Kg /min , there was almost complete cessation of function in all areas measured

The high-flow and low-flow periods each lasted one-half hour giving a total perfusion time of one hour

In the after period all parameters tended to return toward normal levels although there was continued relative suppression of urinary sodium and chloride excretion

These figures represent mean values in ten experiments

It is interesting to note the correlation of these findings with those we obtained in studies of oxygen utilization during by-pass In each case flow rates of 100 ml /Kg /min maintained function at control levels, with marked impairment at low flow rates In attempting quantitation of optimum flow rates it should be recalled that this figure

membrane oxygenator The blood in the first two groups perfused respectively at high and low flow rates was adequately oxygenated. In the third (high flow) and fourth (low flow) groups an inadequate surface area of membrane was used It could not diffuse more than 50% of the oxygen required by the animal It is of interest that the second third, and fourth groups all took up about the same amount of oxygen The difference in survival rate between the first two groups and the latter two groups of animals lay in the profound difference in the degree of acidosis

Despite our efforts to perform the most physiologic perfusion possible the animals of Group I only consumed 82% of their control oxygen uptake This resulted in some hypoxic acidosis which was compensated by a relative respiratory alkalosis More pronounced in the animals of Group II the quantity of lactic acid produced during low flows with an oxygen uptake of only 53% of the control could still be compensated by the buffers and CO_2 reduction However these animals took longer to awaken, for it takes time to correct a metabolic acidosis

Groups III and IV with arterial blood pH values of 6 8 and 6 9 due to a combination of respiratory and hypoxic acidosis did not survive This may be related to an earlier finding in our laboratory that animals in which the brain wave potential is abolished by severe hypercapnea for more than 15 minutes die in a state of normovolemic shock Such was the case with these dogs which were purposely subjected to inadequate oxygenation during perfusion Despite total oxygen uptakes not unlike that of Group II they died in severe acidosis The damage probably lies in the brain but may in part be related to a nonreactive cardiovascular system

DR WILLIAM J KOLFF Cleveland "Late Acidosis After By pass" If someone tells me that his patients treated with the artificial heart lung machine have no acidosis I do not believe him. I do not believe him until I am shown the pH s three or six hours after the operations Figure 132A shows a scatter graph of the data collected on 12 patients during and after open heart operations It may be seen that the pH is lowest three hours after the perfusion when it is no longer corrected by overventilation either by the anesthetist or in the artificial heart lung machine As pCO is low or normal it is not a respiratory acidosis but a metabolic acidosis Figure 132B shows the data on 13 patients in whom we expected an acidosis on the basis of a low circulation as evidenced by hypotension before during or after the cardiac by pass All these patients were given a slow intravenous infusion of 4.5 mEq

body fluids of hydrogen ion initially associated with the products of incomplete oxidation of carbohydrate substances Our data show that the pH changes in a linear function with the venous oxygen saturation and the blood lactate The new hydrogen ion thus arises within the cell itself, apparently on the basis of low flow Intracellular buffers are taken up first and myocardial irritability may be effected very early

This is in sharp contrast to acidosis such as renal acidosis or the acidosis resulting from the infusion of ammonium chloride or fixed acid In these latter situations, the extracellular buffers are taken up first and the changes in the cell occur later

Where is the acid produced which results in hypoxic acidosis? We believe that the liver is an unlikely site Dr Senning told us this morning of experiments which corroborate this opinion Skeletal muscle appears to be the most likely site Why should this muscle produce acid when it is resting? It would be of interest to study the effect of curare in wiping out residual muscle activity under anesthesia, and thus—hopefully—reducing acid production in muscle when exposed to low or borderline blood flow

It is clear that *low flow rate* is primarily responsible for acidosis in pump-oxygenator procedures, acidosis is not in any sense an intrinsic property or inevitable result of the flow circuit or its operation Hypoxic acidosis is easily avoided by adequate perfusion

Relative to Dr Callaghan's data He showed a most interesting thing, namely, that the pump can eliminate carbon dioxide so efficiently as to maintain pH in the face of an increasing hypoxic acidosis Then when the patient comes off the pump and goes back on his own ventilation, returning pCO_2 to 40 mm Hg, a very marked fall in pH results We also have observed this It re-emphasizes the importance of maintaining the pump output at a pCO_2 near normal, so as not to mask underlying metabolic changes

DR GEORGE H A CLOWES, JR, Cleveland I arise again to remark further on the damage of the brain during perfusion and its relationship to survival of the animal We must keep clearly in mind the difference between respiratory acidosis caused by the accumulation of carbon dioxide and the acidosis resulting from the production of organic acids during anaerobic metabolism The latter, Dr Moore has suggested, might best be referred to as "hypoxic acidosis"

To illustrate the importance of brain damage by acidosis, attention is drawn to Table III of our paper on the membrane oxygenator Four groups of animals were subjected to total perfusion for one hour by the

membrane oxygenator The blood in the first two groups perfused respectively at high and low flow rates was adequately oxygenated In the third (high flow) and fourth (low flow) groups an inadequate surface area of membrane was used It could not diffuse more than 50% of the oxygen required by the animal It is of interest that the second, third and fourth groups all took up about the same amount of oxygen The difference in survival rate between the first two groups and the latter two groups of animals lay in the profound difference in the degree of acidosis

Despite our efforts to perform the most physiologic perfusion possible the animals of Group I only consumed 82% of their control oxygen uptake This resulted in some hypoxic acidosis which was compensated by a relative respiratory alkalosis More pronounced in the animals of Group II the quantity of lactic acid produced during low flows with an oxygen uptake of only 53 of the control could still be compensated by the buffers and CO reduction However these animals took longer to awaken for it takes time to correct a metabolic acidosis

Groups III and IV with arterial blood pH values of 6 8 and 6 9 due to a combination of respiratory and hypoxic acidosis did not survive This may be related to an earlier finding in our laboratory that animals in which the brain wave potential is abolished by severe hypercapnea for more than 15 minutes die in a state of normovolemic shock. Such was the case with these dogs which were purposely subjected to inadequate oxygenation during perfusion Despite total oxygen uptakes not unlike that of Group II they died in severe acidosis The damage probably lies in the brain but may in part be related to a nonreactive cardiovascular system

DR WILLIAM J KOLFF Cleveland "Late Acidosis After By pass" If someone tells me that his patients treated with the artificial heart lung machine have no acidosis I do not believe him I do not believe him until I am shown the pH s three or six hours after the operations Figure 132A shows a scatter graph of the data collected on 12 patients during and after open heart operations It may be seen that the pH is lowest three hours after the perfusion when it is no longer corrected by overventilation either by the anesthetist or in the artificial heart lung machine As pCO_2 is low or normal it is not a respiratory acidosis but a metabolic acidosis Figure 132B shows the data on 13 patients in whom we expected an acidosis on the basis of a low circulation as evidenced by hypotension before during or after the cardiac by pass All these patients were given a slow intravenous infusion of 4 5 mEq

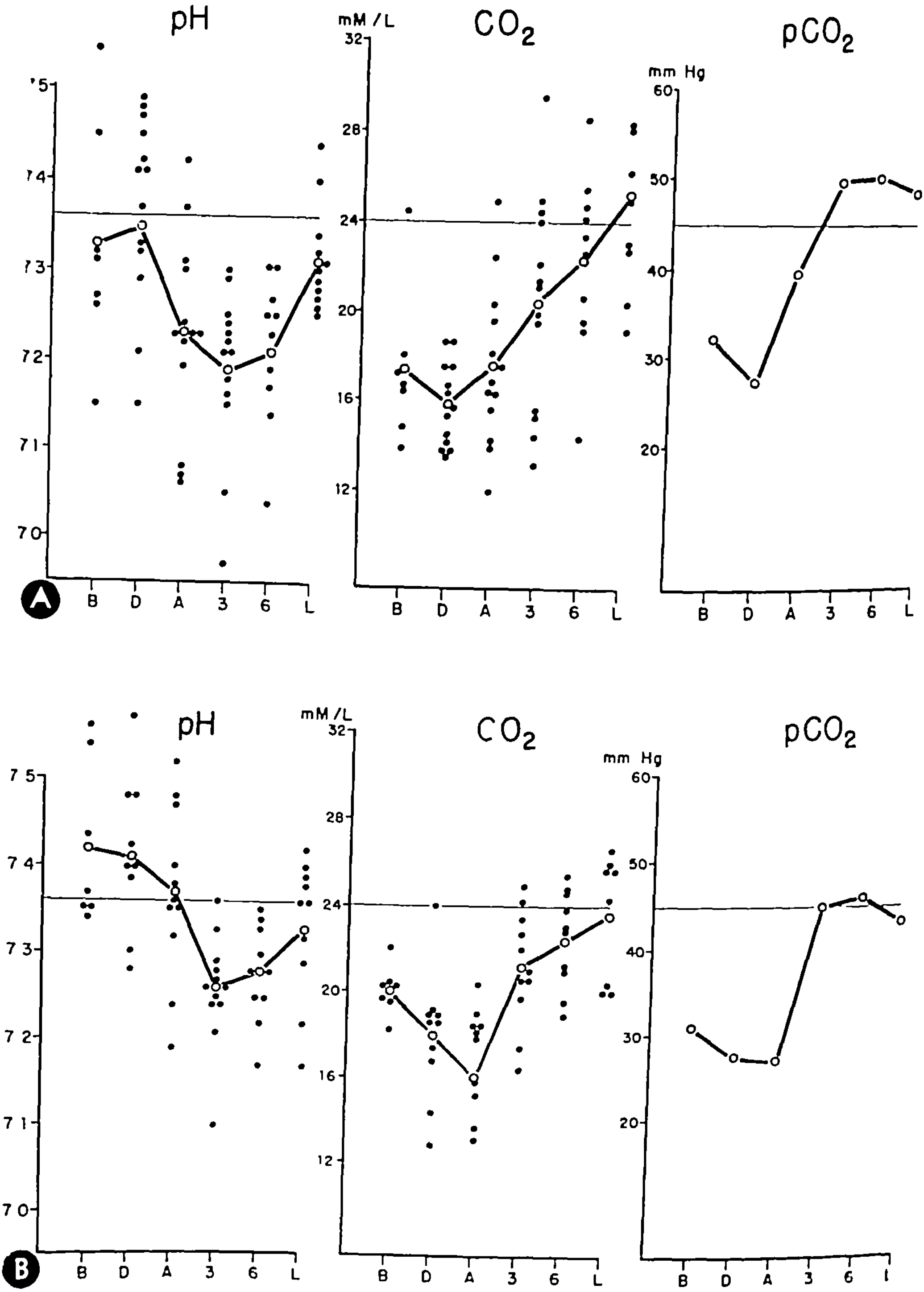


FIGURE 132 A & B (Kolff)

of Na bicarbonate/kg /body weight diluted with a double volume of 5% glucose in water This infusion is set to run in over six hours after surgery but is discontinued when the downward trend of the pH is checked Notwithstanding the administration of the sodium bicarbonate, the low pH three hours after surgery is still evident.

Central venous blood samples for pH and CO_2 are taken from an indwelling polyethylene catheter in the vena cava inferior which during and after the run is also used for the measurement of central venous pressures

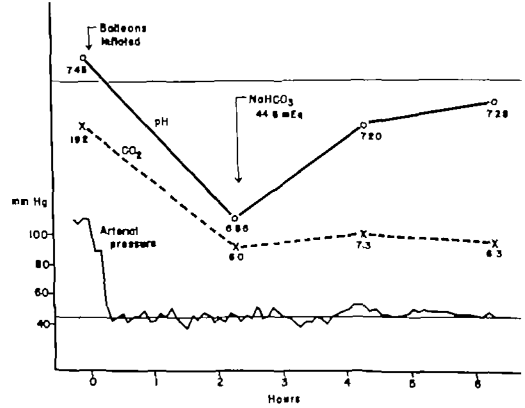


FIGURE 133 (Kolff)

Doctor Iwao* in our laboratory confirmed that the metabolic acidosis which occurs in patients with the artificial heart lung machines is most likely due to nothing else but to the reduction of cardiac output. In dogs balloons were inflated on catheters in the venae cavae to reduce the cardiac output resulting in a mean arterial blood pressure of 45

* Changes in pH and Blood HCO and Their Correction in Patients Undergoing Open Heart Surgery by Iwao W R Faulkner and W J Kolff The Cleveland Clinic Quarterly in press

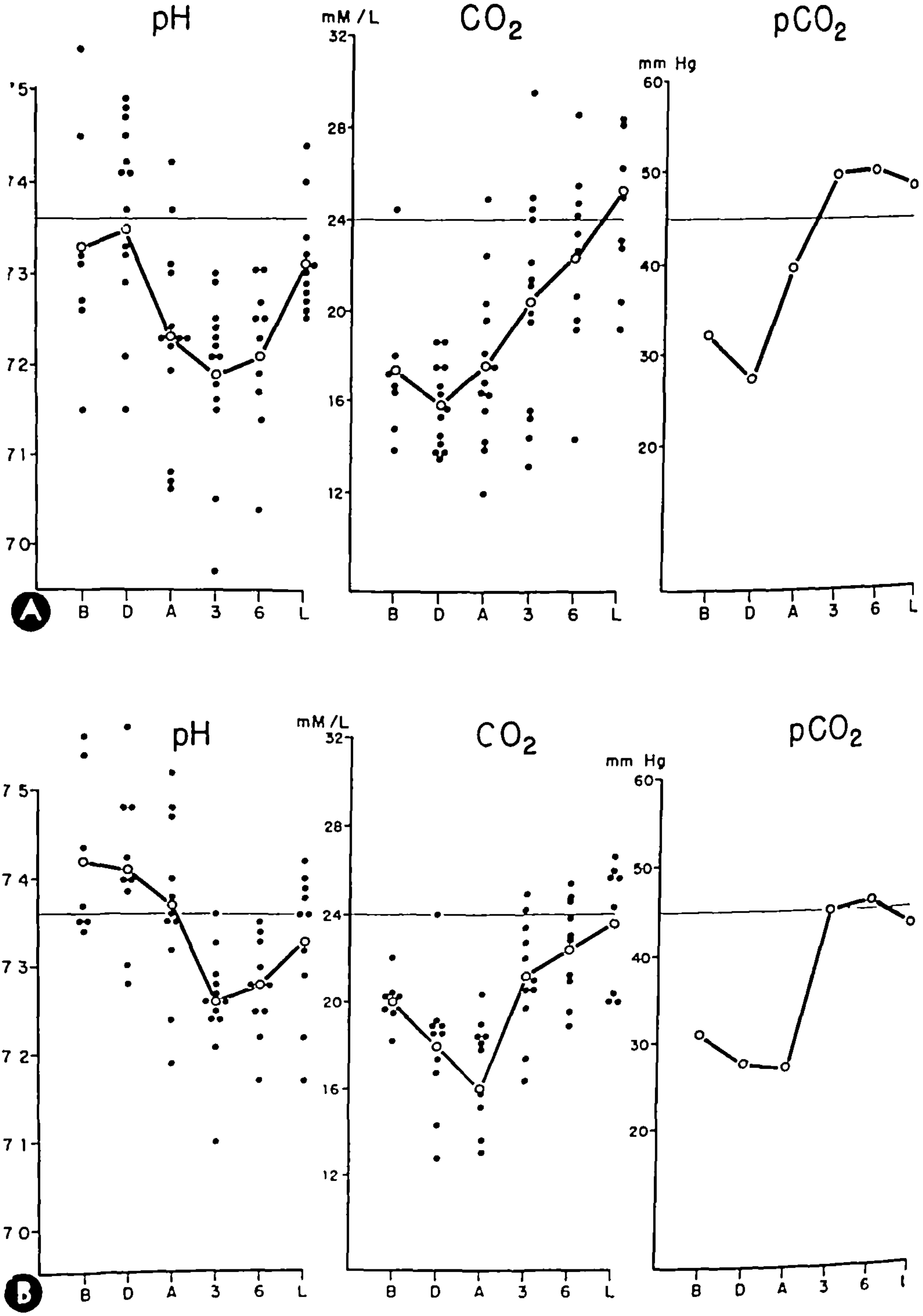


FIGURE 132 A & B (Kolff)

seen during perfusion with the pump-oxygenator While the acidosis in itself may not be harmful during short term by passes it seems as if it might behoove us to know specifically the nature of this acidosis so that we may more accurately maintain the body in normal acid base and fluid-electrolyte homeostasis during extracorporeal circulation

We have perfused and studied a closely controlled series of dogs using a bubble-type oxygenator Figure 134 On this slide we have represented the preoperative lactate levels and the lactate levels at the end of perfusion just before the pump was turned off these have been plotted against the venous oxygen saturations taken at that particular moment The rise we see would be from right to left on the chart The two animals with the highest post perfusion lactate levels were perfused with flows of 25 cc./kg as calculated from gear ratio calibration on the Sigmamotor The two animals with the lowest post

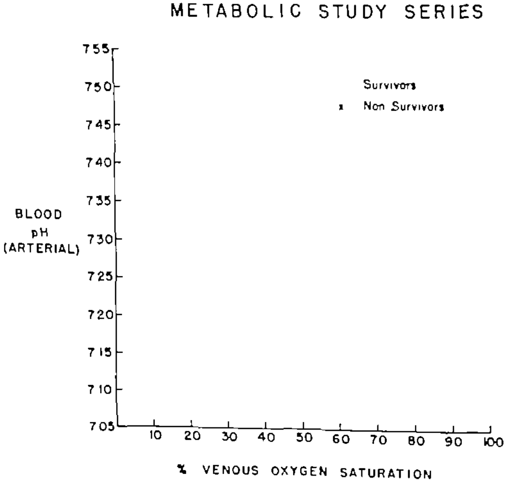


FIGURE 135 (Litwin)

mm Hg All of these dogs developed severe metabolic acidosis In the experiment shown in Figure 133 the pH is corrected by the administration of sodium bicarbonate although the CO_2 stayed low Similar acidosis occurs in patients with reduced cardiac output never treated with artificial heart-lung machines

In summary, acidosis must be looked for not during but many hours after cardiac by-pass Samples are taken from a polyethylene catheter in the inferior vena cava Metabolic acidosis is most likely due to reduced cardiac output and not to any mystic action of artificial heart-lung machines

DR MARTIN S LITWIN, Boston We have been particularly concerned about the development of the "metabolic acidosis" generally

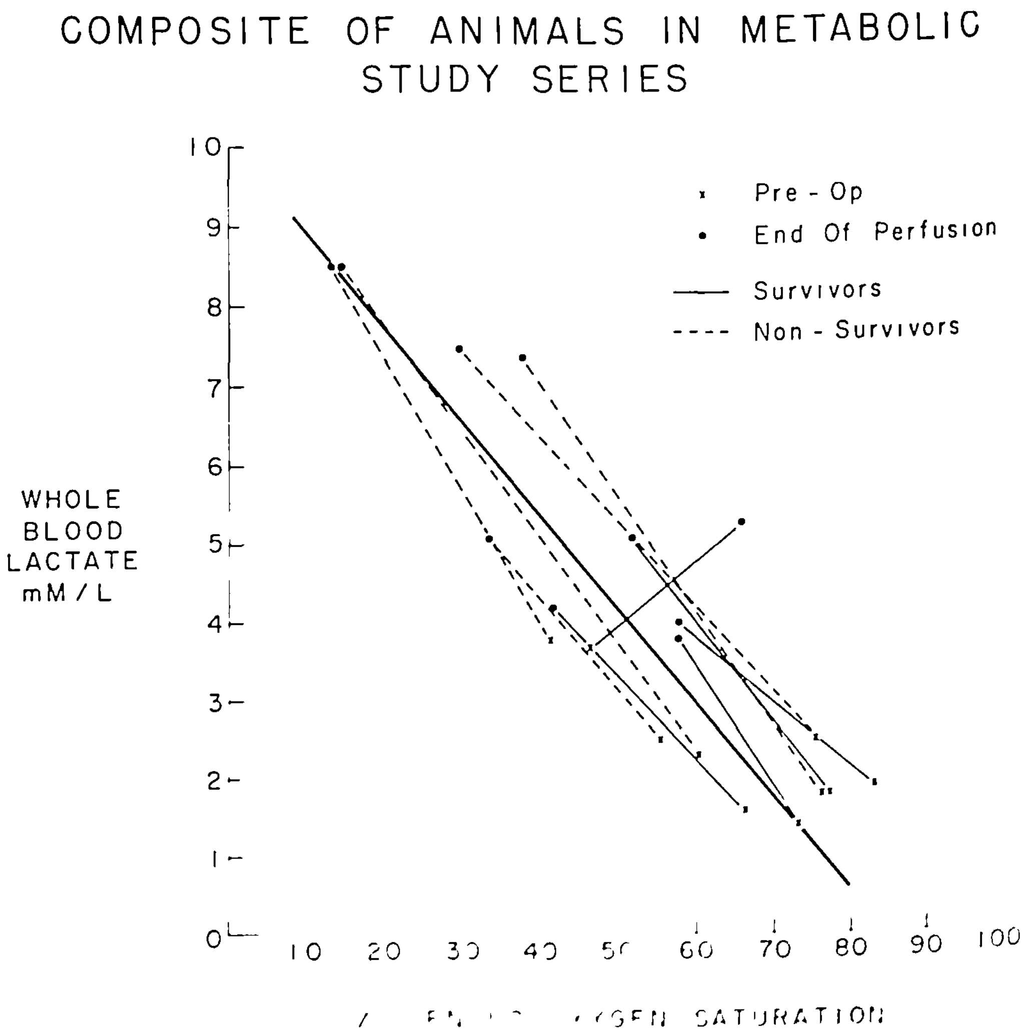


Figure 134 (Litwin)

seen during perfusion with the pump-oxygenator While the acidosis in itself may not be harmful during short term by passes it seems as if it might behoove us to know specifically the nature of this acidosis so that we may more accurately maintain the body in normal acid base and fluid-electrolyte homeostasis during extracorporeal circulation

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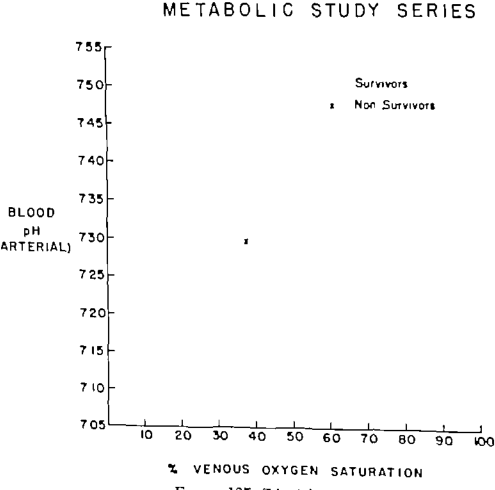


FIGURE 135 (Litwin)

perfusion lactate levels were perfused with flows of 70 cc/kg as calculated on a "rotameter" flowmeter The remaining six animals were perfused with flows ranging between 25 and 70 cc/kg This straight line in the middle of the chart illustrates that there is essentially a linear and inverse relationship between venous oxygen saturation and whole blood lactate level

In Figure 135, we have taken the post-perfusion arterial blood pH and plotted these values against the post-perfusion venous oxygen saturations The latter is a function of flow through the patient and may represent quite closely the oxygen tension of the tissues One can readily see that these points fall in a relatively straight line

Thus, we feel that there is an inverse relationship between venous oxygen saturation and blood lactate level, between blood pH and venous oxygen saturation, and between whole blood lactate concentration and blood pH We have graphically demonstrated that the acidosis seen during low-flow operation of a pump-oxygenator is a "hypoxic acidosis" due to the accumulation of products of incomplete and anaerobic glycolysis These are, as is well known, lactic acid, pyruvic acid, and other related end-products of poor oxygenation It is a by-product of inadequate perfusion

DR HANS C ENGELL, Copenhagen We, too, have seen this drop in pH, and this metabolic acidosis after perfusion as Dr Kolff

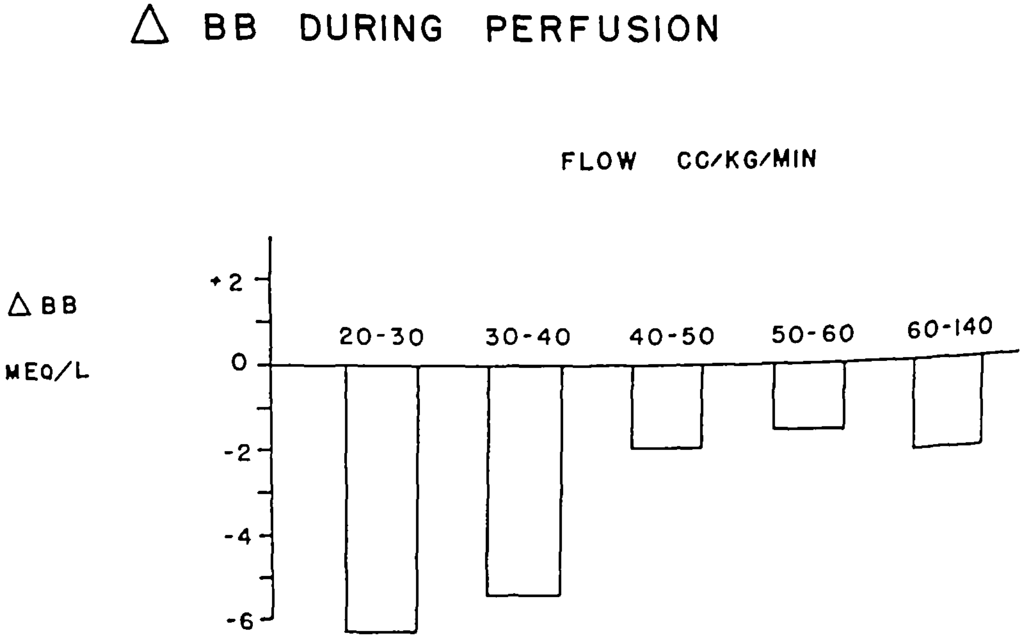


FIGURE 136 (Pontius)

mentioned I think it has nothing to do with perfusion *per se* We have made an incision in the right ventricle and considerably weakened the heart In some cases it was not even possible to correct the defect Especially in the last mentioned cases we have seen a tremendous drop in pH starting immediately after the perfusion and going on for several hours I think it is because of insufficient output of the heart.

DR. ROBERT G PONTIUS Boston Mass We have studied the development of metabolic acidosis during perfusion by determination of whole blood buffer base and pCO values in addition to pH Metabolic acidosis was indicated by a decrease in buffer base

Figure 136 In groups of experimental animals perfusion rates were increased from 20-30 cc/kg/min to 60-150 cc/kg/min. The corresponding average values of change in buffer base ranged from —6 4 mEq/L. to —2.1 mEq/L. We feel that this metabolic acidosis is primarily an

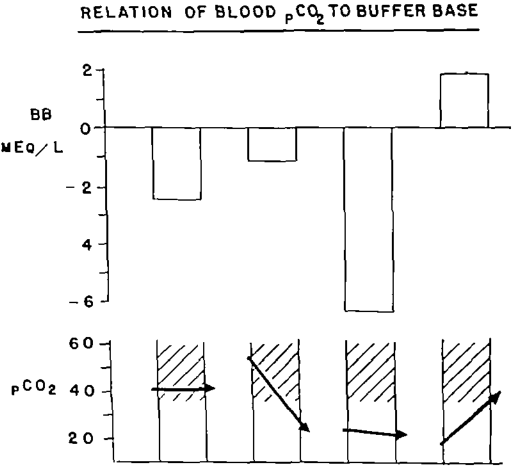


FIGURE 137 (Pontius)

indication of a defect in oxygen transport to the tissues at sub-basal perfusion rates

Figure 137 Animals with perfusion rates 60-140 cc/Kg/min were placed in four subdivisions depending upon the presence of respiratory alkalosis prior to or at the end of perfusion A striking drop in buffer base of 6 4 mEq/L was seen in the subdivision which had respiratory alkalosis both prior to and at the termination of perfusion

Figure 138 Further study of an example of this type was done in an

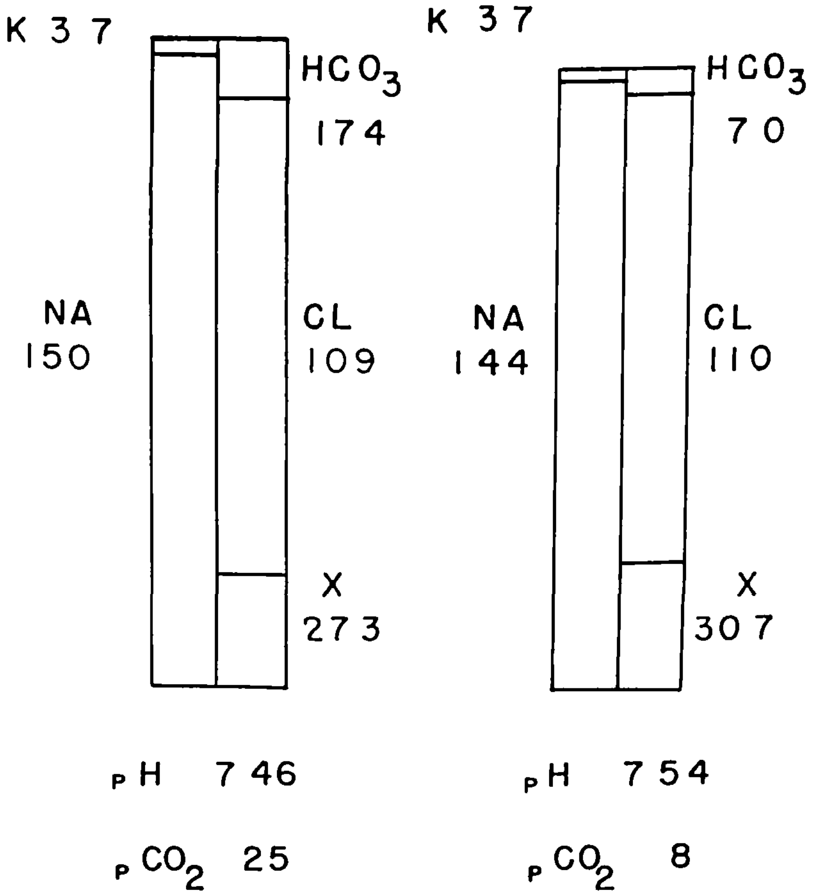


FIGURE 138 (Pontius)

instance where the buffer base value fell 8 mEq/L and the pCO_2 was 25 mm Hg prior to perfusion and 8 mm Hg at its termination The changes in plasma electrolytes indicated an estimated increase of only 3 4 mEq/L in the compartment containing acid radicals, and a drop in sodium concentration of 6 mEq/L Thus in this type of metabolic acidosis the shift of sodium out of the plasma was of a greater magnitude than the accumulation of acid radicals This is in keeping with the concepts of Singer and Hastings (*Medicine*, 27 223-242 1948)

DR HAROLD J C SWAN Rochester It seems to me that the discussion has taken a trend this afternoon which may be worth while stating more clearly We have got a little away from that which is acceptable from a clinical standpoint as judged by the criteria of provision of adequate operating time and survival of the patient These factors are obviously very important but we have evidence of physiological changes with various forms of oxygenators which are compatible with these criteria for satisfactory perfusion I think that it is very important to recognize these changes and to develop technics to identify more subtle alterations in the physiology of the organism during perfusion Only in this way will data accumulate which will permit the design and development of equipment better suited to problems confronting us We had a very interesting paper from Dr Hodges and Dr Lillehei I did not quite get the interpretation of their findings What is the cause of these abnormalities? Were they associated with histologic change?

DR. PAUL HODGES Minneapolis Minn In response to Dr Swan s questions it was the clock which prevented further discussion of results We feel that there is not as yet sufficient information to justify final conclusions but certainly some speculation is possible at this time

I believe that we have shown by this sensitive test that copious quantities of antifoam are unnecessary and may be undesirable due to the excess being washed out of the reservoir chamber Antifoam A is an extremely potent agent in reducing surface tension, active in a concentration of one part in ten million Thus minimal quantities as a thin film only momentarily in contact with the blood are sufficient and compatible with good results This consideration is I believe of importance to all oxygenator users because of the necessity of returning to the perfusion system the blood aspirated from the open heart In a bubble diffusion system such as we utilize no antifoam is used in the cardiotomy return reservoir as a rule because the air bubbles are effectively removed further along the system However in film and membrane type oxygenators careful and rapid debubbling by contact with antifoam silicone of the cardiotomy losses (which we have measured as high as 1500 cc per minute in an adult tetralogy patient even with the heart arrested and the coronary flow cut off) is essential before return to the oxygenator

There has been a surprising amount of interesting discussion upon the subject of oxygen tension at this meeting One of the reasons that

a more sensitive blood brain barrier test was sought for and developed was to investigate this problem We have been unable to find any indication that the oxygen tensions achieved in any of the several types of bubble and film type oxygenators tested had a disturbing effect upon the blood brain barrier, provided the patient and extracorporeal blood are at the same temperature However, we will not consider this aspect of the study finished until we have monitored the perfusions by polarographic measurements This temperature control is important in all oxygenators, whether of bubble, film, or membrane type In numerous reports from this institution the importance of maintenance of body temperature in the extracorporeal circulation has been emphasized Some have construed this emphasis as some prejudice against hypothermia rather than appreciating its full significance Plasma saturated with oxygen at low temperatures will release inexorably oxygen bubbles when perfused into the substantially warmer patient Trapped air bubbles also can be an important problem before the perfusion is started, unless meticulous care is taken to insure that the oxygenator priming blood is at body temperature and is not taken directly out of the icebox We keep a water bath in the operating suite for preliminary warming to body temperature of all blood used for priming or replacement purposes

Pertinent to this discussion of oxygen tension and temperature control we should point out that a recent paper on this subject (Proc Staff Meeting of Mayo Clinic, 32 389, 1957) harbors some obvious misconceptions These authors purported to show that a certain type of bubble oxygenator produced high oxygen tensions (neglecting to mention that oxygenators of all types do likewise) and implied these were dangerous The facts are that all oxygenators (bubble, film, and membrane) produce oxygen tensions in the arterialized blood to about the same degree (which depends upon their efficiency), and considerably higher than normal, because 95 to 100% oxygen is utilized This increased quantity of oxygen is, of course, transported in the plasma Provided the temperature factor, mentioned above, is controlled so that gaseous emboli are not released, no one to date has brought forth any objective evidence that these higher oxygen tensions are harmful within the time limits of exposure likely during a by-pass procedure Further scrutiny of this problem, however is certainly pertinent since oxygen tensions can be kept lower if necessary

Nonetheless and this I would emphasize, Doctor Lillehei believes paradoxically that many of the complex membrane and film type oxygenators which are difficult or even impossible to heat, and which in

some cases have recirculating pumps for the already oxygenated blood are far more dangerous to the patient from the standpoint of air embolism than is a well designed bubble oxygenator in which it is easy to maintain the extracorporeal blood at body temperature and recirculating pumps are not needed nor used

Finally I am sure that small particles of fibrin will continue to be a problem until better arterial filters are available

In regard to the correlation of results on the blood brain barrier study with histologic changes all of the brains are undergoing detailed study by our neuropathologist This portion of the study to be of any value is of necessity laborious and is still in progress Preliminary results available do not indicate any detectable changes suggesting again that this is a physiologic test and is not necessarily associated with histologic changes

THE HEART

SECTION IV

MYOCARDIAL METABOLISM*

By

RICHARD J BING, M D

METABOLISM OF THE ARRESTED HEART

METABOLIC studies on the arrested heart have assumed interest because of the introduction of surgery on the arrested human heart in addition an estimation of the oxygen consumption of the arrested heart permits a more accurate evaluation of myocardial efficiency of the beating organ In previous calculations of myocardial efficiency values for the oxygen consumption of the beating heart were used without making allowance for the basal myocardial oxygen consumption [1,2] If the oxygen usage of the arrested heart represents an appreciable fraction of that of the beating organ then previous figures on myocardial efficiency have been too low since the oxygen usage of the arrested heart was neglected in these calculations Lorber and Gregg have previously obtained information on the oxygen usage of the perfused, arrested and fibrillating heart [3,4] The former found that the oxygen usage of the fibrillating heart exceeds that of the rhythmically contracting organ by about 40% [3] Gregg and his co-workers found that the oxygen usage of the arrested heart amounted to about 16-40% of the working heart with normal sinus rhythm [4]

The subject of metabolism of the arrested and fibrillating perfused heart was reinvestigated with a technique which eliminated opening of the chest and intubation of the coronary arteries [5] After insertion of the catheter into the coronary sinus under

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From the Department of Medicine Washington University School of Medicine and the Washington University Medical Service Veterans Administration Hospital, St Louis, Missouri

Work supported by U.S Public Health Service Grant No H 2678 The American Heart Association and the Life Insurance Medical Research Fund

fibrillating and arrested organ In some instances the glucose concentration in coronary vein blood exceeds that in the arterial perfusate by more than 70 mg %

The observation that the oxygen usage of the empty rhythmically contracting fibrillating and arrested heart is relatively high (20-30% of that of the naturally perfused heart *in situ*) necessitates a re-evaluation of the calculations of myocardial efficiency This fact has already been stressed by Gregg [4] It appears likely that myocardial efficiency of the beating heart is considerably greater than had been previously assumed

The technic described above was also utilized in examining the effect of interrupting the coronary circulation on the oxygen and substrate usage of the heart It has been reported that the heart can remain without blood supply for almost an hour without apparent damage [8] Studies were performed on the arrested heart with coronary perfusion interrupted for periods ranging from thirty minutes to four and one half hours Control observations were carried out on myocardial substrate and oxygen utilization immediately after cardiac arrest had been induced Two relevant observations were made with this technic (a) coronary circulation is greatly altered during cardiac arrest, and (b) the oxygen usage of the heart increases slightly up to two hours after cessation of the coronary circulation After that period, it declines and four hours after interruption of the coronary circulation the heart ceases to utilize oxygen. The altered state of coronary circulation during cardiac arrest was first suspected from the observation that blood withdrawn from the coronary sinus seemed to originate from blood contained in the cardiac chambers or the pulmonary veins In addition when Dextran was added to the coronary perfusate the ratio of Dextran in the perfusate to that in the coronary sinus blood frequently exceeded unity this indicates mixture of blood from sources other than the perfusate Finally histologic studies employing special stains for red cells suggest the opening of previously non visualized capillaries in heart muscle following cardiac arrest The observation that myocardial oxygen utilization increases up to two hours after cessation of coronary circulation illustrates that the heart can incur an oxygen debt provided the respiratory enzymes are intact

fluoroscopic control, a catheter was placed into the femoral artery. The coronary blood flow was then measured with the nitrous oxide method and samples of blood were drawn from the coronary sinus and the femoral artery for the determinations of substrates.[1] A special triple lumen catheter was inserted into the left internal carotid artery and the tip of this catheter was advanced to the aortic valve. The purpose of this catheter was to perfuse all the coronary arteries of the animal through the sinus of Valsalva. Thus, escape of the blood into the aorta and the left ventricle had to be prevented. This was accomplished by two inflatable balloons attached to this catheter, one balloon designed to obstruct the aorta distal to the sinus of Valsalva, the other acting as a barrier to blood flow from the aorta into the left ventricle through the leaking aortic valve. A metal lumen catheter was then introduced into the right atrium through an external jugular vein. The purpose of this catheter was to suction blood from the atrium at the commencement of perfusion, thus keeping the cardiac chamber empty. Cardiac rhythm was monitored through an electrocardiogram. The triple lumen catheter was then advanced through the aortic valve into the left ventricle and the two balloons were inflated. Perfusion of the sinus of Valsalva was carried out with a Sigmamotor pump and blood flow maintained at approximately 40 cc/minute. The volume of inflow was graphically recorded with a recording rotameter. The arterial blood, pump perfusate, and coronary sinus blood were analyzed for oxygen, pyruvate, lactate, glucose and ketone bodies. Cardiac arrest was accomplished by the injection of KCl into the sinus of Valsalva, this induced first several minutes of fibrillation during which studies could be carried out.

The results utilizing this method reveal that there is no statistical difference in the oxygen usage of the empty rhythmically contracting heart and the fibrillating or arrested organ.[5] The oxygen usage in these preparations varies between 20-30% of that of the naturally perfused organ *in situ*. This suggests that the oxygen usage of the heart is primarily determined by its external work. Usually the non-beating perfused heart extracts glucose, pyruvate, lactate, and ketone bodies from the perfusate.[1, 2] However, some metabolic disturbances are encountered in the perfused

shown the great versatility of the myocardium which is able to utilize almost all known substrates circulating in the blood

The effect of anoxia on the metabolism of the arrested heart has been dealt with in a preceding paragraph The response of the beating heart to ischemia or anoxia is remarkably uniform varying only in degree with the severity of the ischemia For example in hemorrhagic shock the degree of ischemia is relatively minor and the metabolic changes are few [8] The most severe changes are seen in ventricular fibrillation [9] It is very likely that in hemorrhagic shock the metabolic alterations occurring in the heart muscle are very similar to those occurring in other portions of the body particularly in skeletal muscle [8] The most significant change is a diminution in myocardial pyruvate usage with an increase in that of lactate In most instances pyruvate levels in coronary vein blood exceed those of arterial blood in both the oligemic and normovolemic phases of shock The fact that lactate usage by the heart is not interfered with in hemorrhagic shock, indicates that under these conditions the heart muscle is not forced to rely on anaerobiosis for energy production

In experimental coronary occlusion on the other hand the lactate concentration of coronary vein blood frequently exceeds that in arterial blood indicating glycolysis [10] Since myocardial infarction leads to early coagulation necrosis enzymes from the destroyed and dying cells are released into the blood stream and their activity can be detected in peripheral blood [10] Thus plasma activities of malic acid dehydrogenase phosphohexose isomerase fructose aldolase and glutamic oxalacetic transaminase rise within two hours following embolization and reach a peak after twenty four hours

In congestive failure metabolic alterations are absent [11] Thus myocardial oxygen consumption does not differ from that obtained in normal individuals and substrate utilization appears to be equally normal [1] However energy utilization is seriously interfered with in congestive failure When bands of contractile proteins (actomyosin) are prepared from failing human heart muscle obtained at autopsy a marked diminution of contractility is found This is in agreement with the observation of Benson who had previously noted some difference in the protein composition in

The resistance of respiratory enzymes in the arrested heart in which the coronary circulation is interrupted is more than matched by the resistance of the contractile proteins of heart muscle. It could be shown that when the contractile protein (actomyosin) is prepared from one to six hours after death of the patient, no significant differences in contractility can be demonstrated.[7] Tests for differences among these groups were not significant ($p >$ than .05) nor were the differences among their regression coefficients ($p >$ than .05). Apparently, the contractile proteins of heart muscle preserve their contractility as late as six hours after death. The main factor responsible for irreversible cessation of cardiac activity at the operating table is neither loss of contractility of the proteins nor death of the respiratory enzymes, but an irreversible change in the membrane of the muscle fiber with loss of normal conductivity and rhythmicity.

METABOLISM OF THE BEATING HEART

In these studies the technic of coronary sinus catheterization was utilized.[1,2] This has the disadvantage that individual catalytic enzyme systems cannot be explored. But these studies are carried out under physiological conditions without interruption of the continuity of the internal environment. Studies on the human heart have indicated that it can utilize considerable quantities of carbohydrates, fatty acids, ketone bodies, and amino acids.[1,2] Assuming complete oxidation of carbohydrates, the aerobic metabolism of these foodstuffs in man could account for only approximately 35% of the total myocardial oxygen uptake. The main contribution of the oxidative metabolism of the heart, therefore, is derived from non-carbohydrate material. Myocardial uptake of fatty acids is particularly great after a high fat intake,[1,2] this suggests the possibility of storage of fatty acids within the heart muscle. It is likely that this constitutes an effort of the heart to guard its energy production against a sudden decline in fuel supply, primarily carbohydrates. The human heart also extracts considerable quantities of amino acids and after infusion of a protein hydrolysate as much as 40% of the total oxygen uptake of the heart can be accounted for by catabolism of these substrates.[1,2] The results obtained on the human heart in vivo have

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heart muscle of dogs with chronic failure compared to that of heart muscle from normal dogs.[12] Among these differences was a decrease in concentration of actomyosin, diminished viscosity per unit of actomyosin and decreased viscosity of response upon addition of ATP. These changes were ascribed to alterations in organizations of actomyosin, more specifically to the presence of myosin uncombined with actin. This dissociated state of actomyosin may be due to physical changes in heart muscle. Olson concluded that heart failure in dogs leads to marked changes in the physical-chemical properties of myosin consistent with sizable increases in molecular weight.[13] Regardless of whether diminished contractility of actomyosin obtained from failing hearts is due to dissociation between actin or myosin or due to physical-chemical changes of myosin alone, it is likely that myocardial failure is the result of or is accompanied by a defect in the organs of energy utilization of the myocardium, the contractile proteins.

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was also given to the volume of blood flowing through the bronchial arteries returning to the left atrium through the pulmonary veins This flow has been estimated by Bruner and Schmidt[3] not to exceed 1.25 per cent of the cardiac output under normal circumstances However in the presence of chronic lung disease[4] or the tetralogy of Fallot[5] there may be an enormous increase in the bronchial collateral circulation and thus a great increase in the volume of bronchial venous return to the left atrium

With the right heart by pass preparation experiments were designed to study the coronary flow under conditions that might be expected to occur during open heart surgery Hilton and Eichholtz[6] found in a careful study of the coronary flow in 1925 that the coronary vessels were extremely susceptible to anoxia A fall of oxygen saturation below 20 per cent was found to cause maximal dilatation of the coronary vessels with increase in flow up to 500 per cent As hypoxia or anoxia might readily be expected to occur in open heart surgery a study of the effect of hypoxia on the coronary flow in the right heart by pass experiment was undertaken and results corresponding to those of Hilton and Eichholtz were found[7] There was only a modest increase in coronary flow when the oxygen saturation of the blood was above 70 per cent Below this point the coronary flow increased rapidly With severe hypoxia a rise in coronary flow to as high as 690 per cent of the control values were observed After prolonged anoxia the blood pressure and cardiac output decreased and the coronary flows likewise decreased (Figure 139)

Studies were also made on the effect of vasopressor drugs on coronary flow As these drugs may be used during open heart surgery it was important to study the magnitude of the increase in coronary flow incident to the rise in aortic pressure and change in coronary vessel diameter A marked increase in coronary flow followed the administration of both arterenol and Neosynephrine (Figure 140) The rise in flow was temporary and promptly returned to normal following discontinuance of the drug

As a result of these experiments with right heart by pass it appeared that normal coronary flow as estimated for the intact circulation, could be expected On the other hand should hypoxia

CORONARY BLOOD FLOW DURING BODY PERFUSION*

By

WILLIAM W. L. GLENN, M.D., THOMAS O. GENTSCH, M.D., BERT K. KUSSEROW, M.D., RAYMOND K. BOPP, M.D., *and* MICHAEL HUME, M.D.,

with the technical assistance of

THERESA GRILLO

ONE OF the problems that confronts the surgeon operating on the open heart is the supply of blood to the heart itself. Experiments were carried out in this laboratory in 1951 to determine some of the characteristics of the coronary venous return.[1] In these experiments the venous return was removed from the cava through a single cannula and from the right heart through a second cannula and then passed through a mechanical pump and directed into the pulmonary artery. The main pulmonary artery was securely ligated and ligatures were tied around the cavae and the contained cannula at the junction of the cavae with the auricle to complete the isolation of the right side of the heart. The coronary blood was removed through the cannula placed in the right atrium and ventricle and was collected for direct measurement during brief periods, in calibrated burette.

"Normal" coronary flows measured in the manner described, ranged from 44 to 66 cc. per minute per 100 grams of total heart weight. When expressed in terms of per cent of cardiac output (total flow) the range was 3.3 to 6.7 per cent. These results were in accord with the values reported by Eckenhoff, Hafkenschiel and Landmesser.[2] At the time of our early experiments, consideration

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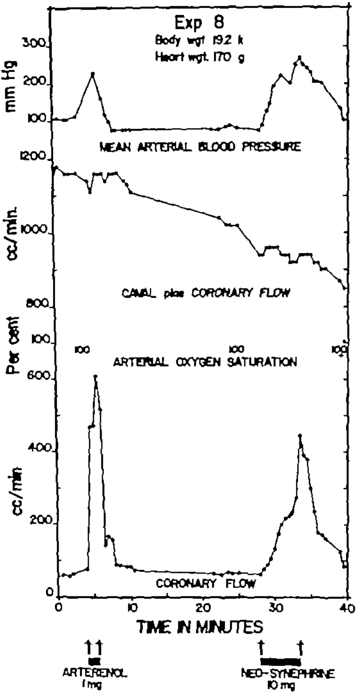


FIGURE 140

METHODS

The measurement of coronary flow and cardiac output is wit a few changes identical to the technic described in experimen with by pass of the right heart The technic used is as follows

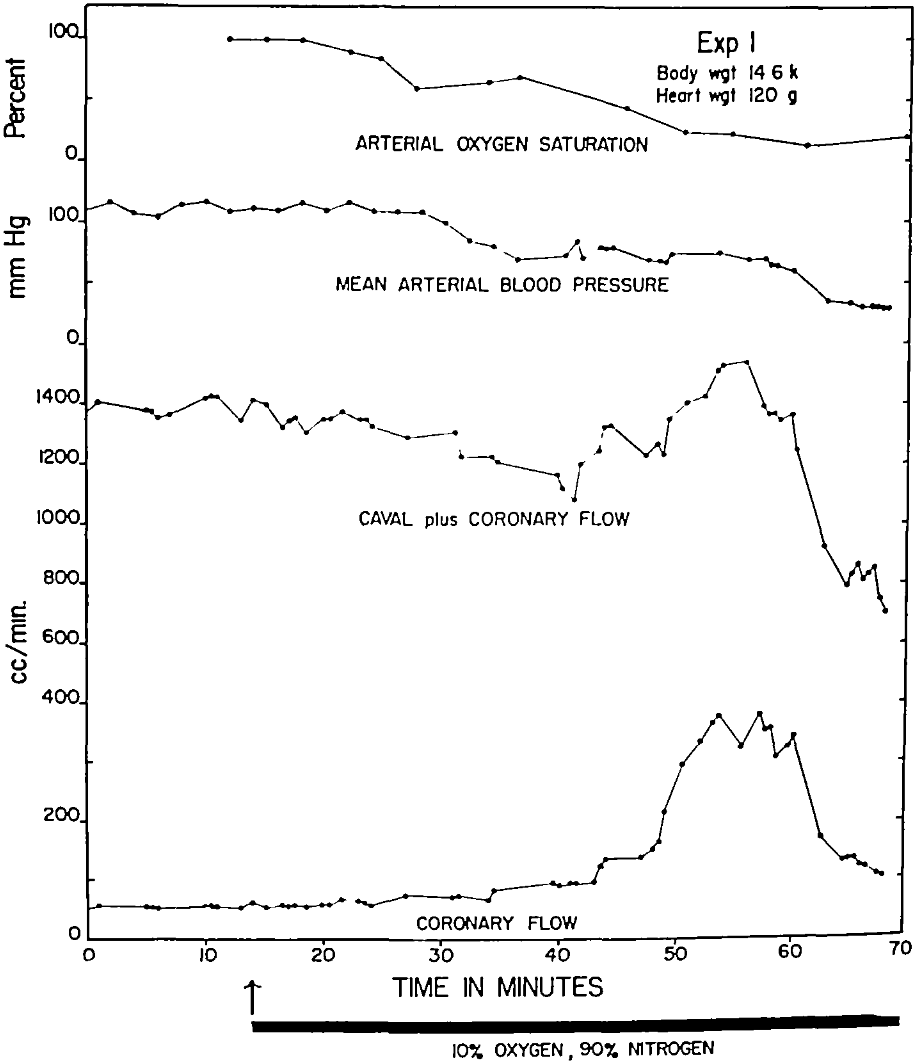


FIG 139 From Maraist, F B and Glenn, W W L, *Surgery 31* 146, 1952 Permission of the Publisher

occur or adrenergic drugs be given during the course of an open heart operation, exceedingly high coronary flows might be encountered making surgery within the open heart difficult or impossible

Since these early experiments on coronary flow with bypass of the right heart, several extra corporeal oxygenators have become available for general use and further studies on coronary flow with total by-pass of the heart and lungs have been reported[7, 8] Further experiments on coronary flow with total by-pass have also been carried out in this laboratory

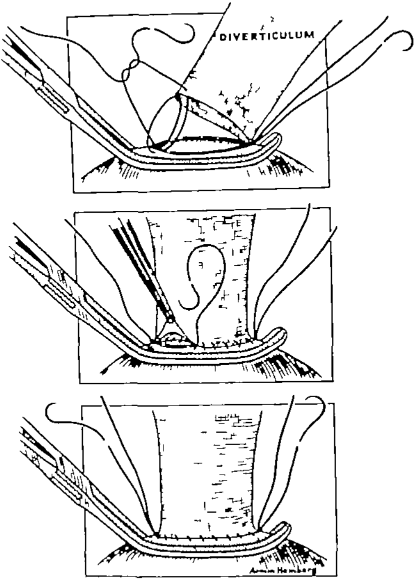


FIGURE 141

being pumped out into the pulmonary artery the previously placed ligature around the main pulmonary artery is securely tied

The coronary flow can be directed into a burette and measured for short periods or allowed to flow directly into the pump oxygenator With "Normal" flows ten to twenty second collections of coronary flow are the rule but when flow becomes excessive shorter collection periods are necessary Usually seventy five to one hundred and occasionally as many as one hundred and fifty

Mongrel dogs are anesthetized with nembutal and after intubation of the trachea the right pleural cavity is opened through the bed of the fourth rib The pericardium is incised and the superior vena cava is surrounded central to the azygos vein The inferior cava is likewise surrounded just distal to the right atrium Heavy silk sutures are placed but not tied around these vessels The aorta is then separated over a short distance from the pulmonary artery and another heavy silk suture is placed but not tied around the main pulmonary artery The lumen of the ascending aorta is then partially occluded and an incision about one and a half centimeters in length is made through the wall of the occluded portion. A rubberized fabric tube about 10-14 centimeters long and one and one half centimeters in diameter is sewed to the incision in the aorta (Figure 141) Blood is allowed to fill the tube temporarily to detect the presence of a leak at the suture line If a leak is found, extra sutures are placed to correct it This tube will serve as the arterial inflow when it is attached to the arterial circuit of the pump-oxygenator A purse string suture is then placed in the right atrium near but not at the junction with the superior vena cava A small incision is made in the atrium within the confines of the purse string and a plastic cannula (16-18 French) with multiple perforations near the tip is then inserted into the auricle and passed well up into the superior cava A similar cannula (18-20 French) is passed through a second incision into the inferior vena cava and held firmly in place with a purse string suture

The venous cannulae are then attached to the pump-oxygenator and the arterial inflow tube is tied securely in the rubberized fabric tube sutured to the ascending aorta (Figure 142) The pump is then started The ligatures around the superior and inferior venae cavae are tightened around the cannulae to insure the passing of all of the caval flow through these cannulae with no escape of caval blood into the right atrium The tip of the right atrial appendage is then opened and a plastic cannula with many perforations near its tip is passed into the right atrium and into the right ventricle This cannula is attached to a "Y" connector with connections to both the measuring burette and the venous pump of the oxygenator To prevent any of the coronary return from

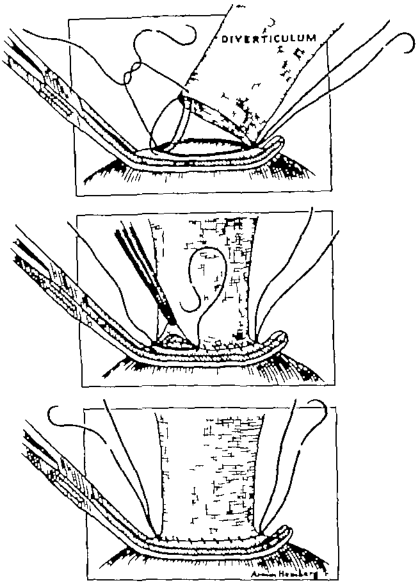


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flow determinations are made during the course of one experiment

Total flow is measured by a Venturi type flow meter placed in the outflow tubing of the pump oxygenator This simple apparatus for measuring total flow is reasonably accurate and easy to calibrate We have tried other flow meters but have returned to this simple device

Two different pump oxygenators were used in these experiments One of these, described by Kusserow,[9] oxygenated the

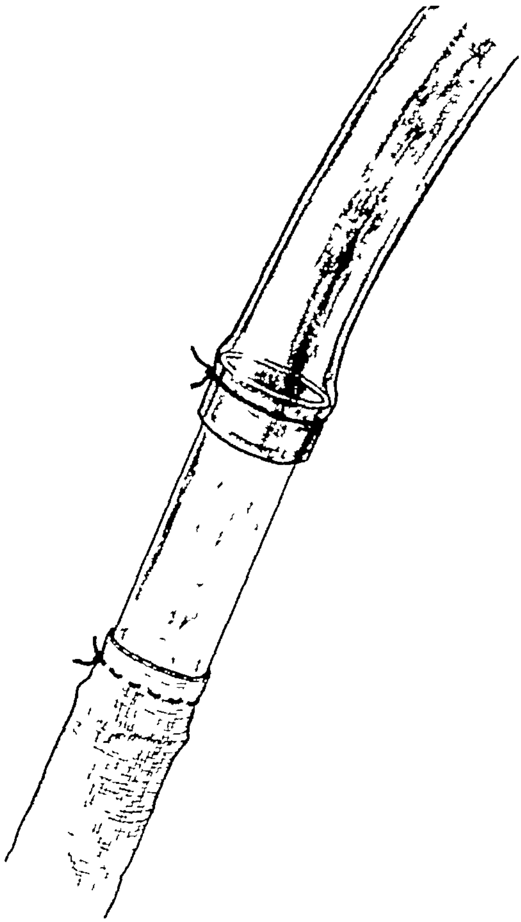


FIGURE 142

blood by means of micro bubbles which were then removed in a centrifuge The pump was of single roller type with wide bore tubing The second oxygenator was of the membrane type described by Clowes [10] The pump used with this oxygenator was of the multiple finger compression type (Sigmamotor)

RESULTS

These experiments are still in progress and although the results reported are valid for the experiments performed thus far confirmation of these preliminary findings is necessary before a final report will be made

Control ("Normal") Coronary Flows Prior to any manipulations a number of observations on "normal" coronary flow were made The results of these studies are recorded in Table I The per cent of total flow for these experiments with total by pass of the heart are compared with four experiments in which coronary flow studies were made with by pass of the right heart only The findings in the two groups of experiments are nearly identical (Table I)

The Influence of Hypoxia on Coronary Flow Generalized hypoxia was produced by the introduction of a 10 per cent oxygen and 90 per cent nitrogen gas mixture into the oxygenator in place of 100 per cent oxygen The effect on coronary flow was similar to that previously observed in the right heart by pass experiment (Figure 143) However because the influence of the low oxygen mixture from the oxygenator was more promptly reflected in changes in arterial oxygen saturation than was the same mixture given to the animal to breathe in the right heart by pass experiments it was possible to shift back to 100 per cent oxygen in the oxygenator before the animal deteriorated from oxygen want. As shown in the graph the coronary flow continued to rise after the return to 100 per cent oxygen and moderately elevated coronary flow persisted for the remainder of the perfusion, one hour after the low oxygen mixture had been discontinued and forty five minutes after the arterial blood was fully saturated.

Anoxia limited to the heart developed following the occlusion of the ascending aorta immediately above the level of the ostia of the coronary arteries The occlusion was continued for fifteen minutes and during this time no coronary flow occurred The heart was allowed to continue beating and after nine minutes ventricular fibrillation began and continued until the heart was defibrillated seven minutes after removal of the aortic occlusion As shown in the graph (Figure 144) on release of the clamp the

flow determinations are made during the course of one experiment

Total flow is measured by a Venturi type flow meter placed in the outflow tubing of the pump oxygenator This simple apparatus for measuring total flow is reasonably accurate and easy to calibrate We have tried other flow meters but have returned to this simple device

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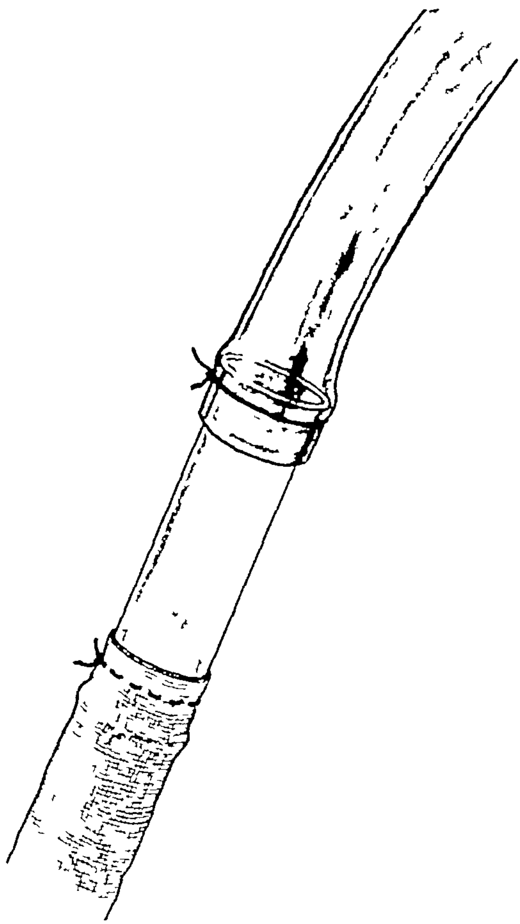


FIGURE 142

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TABLE I

Exp	Weight: Body (kg)	Weight: Heart (gm)	Arterial O_2: Saturation (per cent)	Arterial O_2: pH	Consecutive Observations: Number	Consecutive Observations: Total Time (min.)	Mean Arterial B P: Range (mm Hg)	Mean Arterial B P: Average (mm Hg)	Total Blood Flow: Range (cc per min)	Total Blood Flow: Average (cc per min)	Coronary Blood Flow: Range (cc per min)	Coronary Blood Flow: Average (cc per min)	Coronary Blood Flow: Average Per 100 gm of Heart	Coronary Blood Flow: Per Cent of Total Flow
Rt Heart By-pass														
1	14.6	120	90	7.10	8	11	12	111	82	1,302	5	53	46	3.9
3	10.7	107	92	7.01	8	9	8	122	63	1,035	10	130	66	6.7
4	12.8	95	100	7.13	8	11	12	101	139	1,256	8	42	44	3.3
5	10.3	80	100	7.13	8	7	14	105	104	1,102	11	49	40	4.4
Total Body Perfusion														
K2	14.7	136	97	7.20	9	9	8	113	120	861	20	47	35	4.7
K4	14.6	161	90		10	13	15	117	370	1,387	10	57	36	4.1
K5	18.7	162	94	7.30	7	7	10	98	100	1,565	10	67	41	4.3
K6	18.7	163	98	7.10	11	9	10	102	30	1,180	24	73	50	3.1

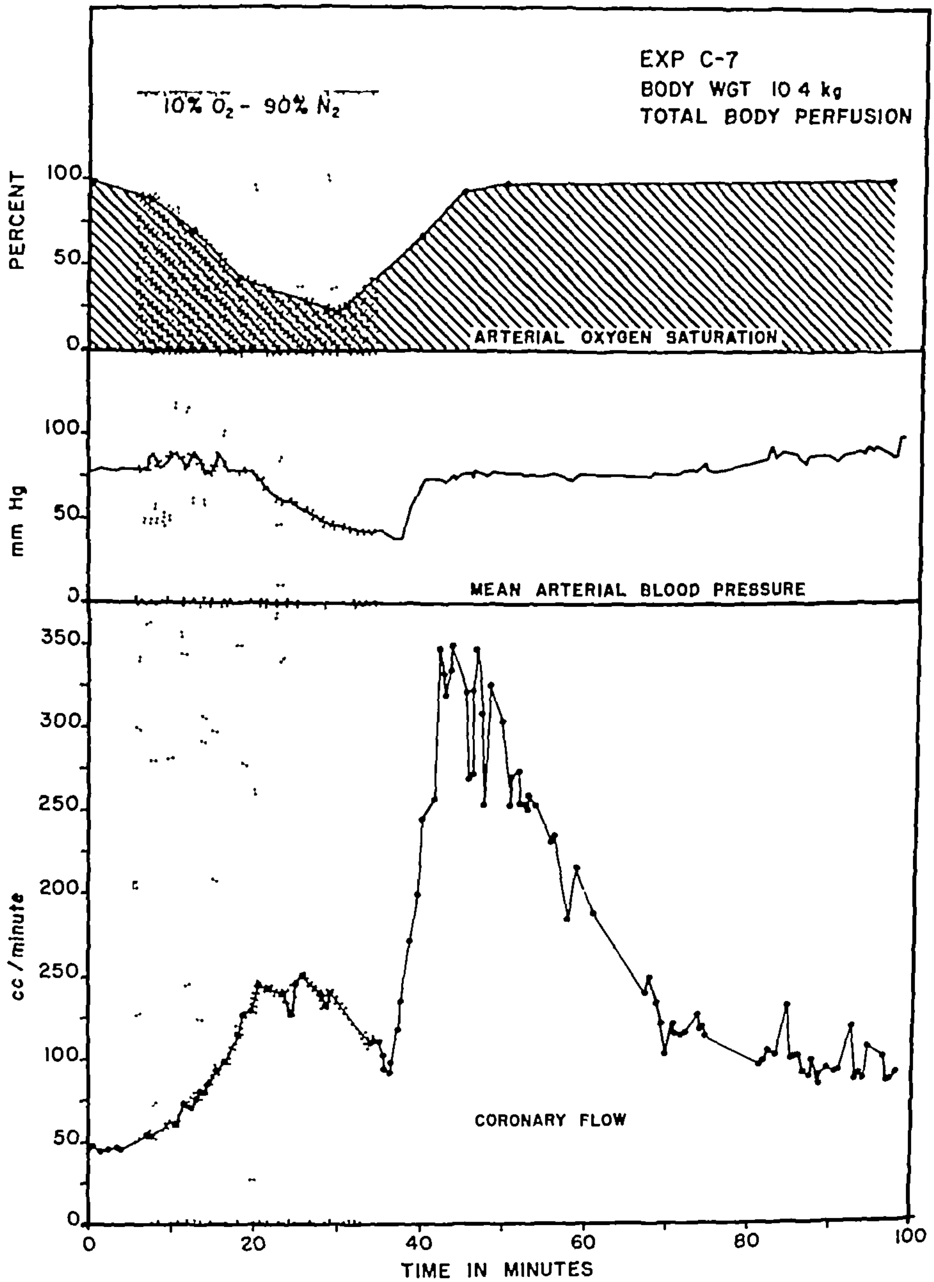


FIGURE 143

coronary flow became exceeding profuse, reaching 80 per cent of the total flow (Figure 145) at one time and continuing at a high proportion of the total flow until the animal began to deteriorate about forty minutes later Coronary arteriovenous differences were studied in this experiment and indicated a marked decrease, most evident in the sample taken soon after the clamp on the aorta was

TABLE 1

Exp	Weight: Body (kg)	Weight: Heart (gm)	Arterial O: Saturation (Per Cent)	Arterial O: pH	Consecutive Observations: Number	Consecutive Observations: Total Time (min.)	Mean Arterial B P: Range (mm Hg)	Mean Arterial B P: Average (mm Hg)	Total Blood Flow: Range (cc per min)	Total Blood Flow: Average (cc per min)	Coronary Blood Flow: Range (cc per min)	Coronary Blood Flow: Average (cc per min)	Coronary Blood Flow: Average Per 100 gm of Heart	Coronary Blood Flow: Per Cent of Total Flow
Rt Heart By-pass														
1	14 0	120	90	7 10	8	11	12	111	82	1 302	3	33	40	3 0
3	10 7	197	92	7 01	8	9	8	122	63	1 033	10	130	60	0 7
4	12 8	93	100	7 13	8	11	12	101	138	1 238	8	42	44	3 3
5	10 3	80	100	7 13	8	7	14	103	104	1 102	11	40	40	4 4
Total Body Perfusion														
K2	14	136	97	7 20	0	9	8	113	120	801	20	47	33	4 7
K4	14 6	101	90		10	13	15	117	370	1 387	19	57	36	4 1
K3	18 7	102	94	7 30	7	7	10	98	100	1 563	10	67	41	4 3
K6	18 7	165	98	7 19	11	0	10	102	30	1 480	24	75	50	5 1

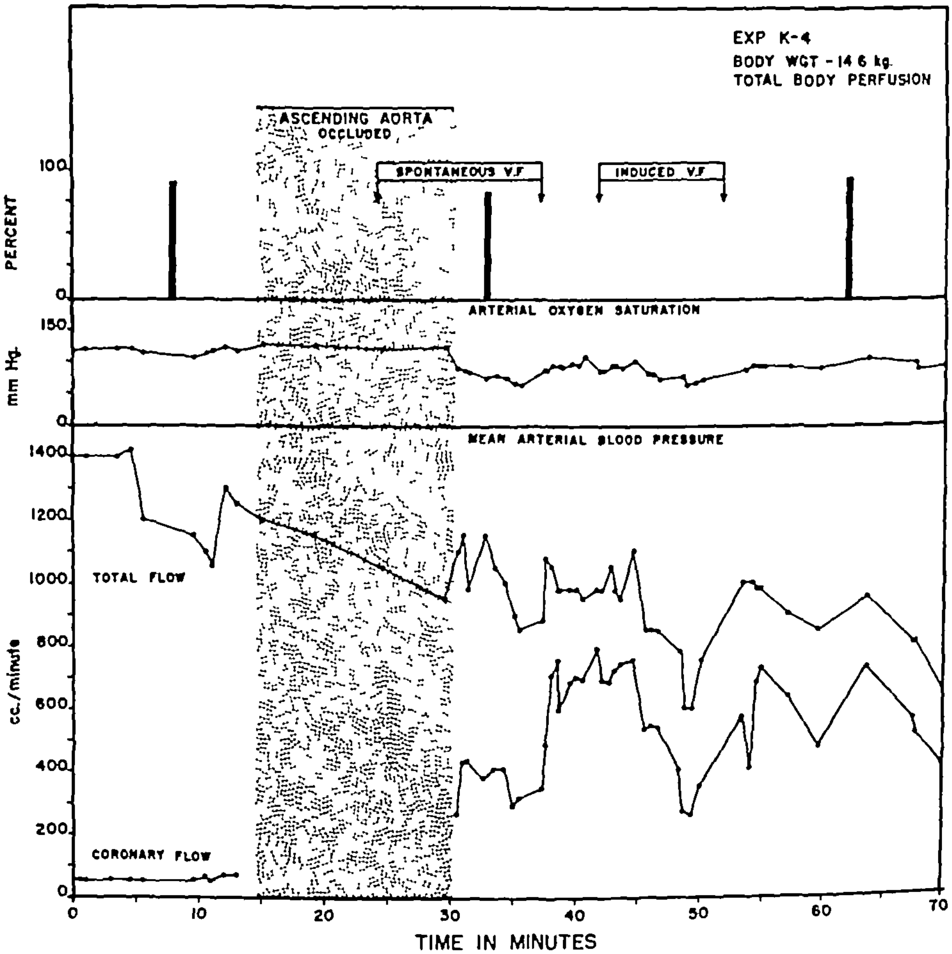


FIGURE 144

released It is interesting too, that the arterial lactic acid value, although moderately elevated when determined before the perfusion began, did not change appreciably throughout the period of perfusion In other experiments, shorter periods of occlusion of the ascending aorta (two–three minutes) were followed by a more moderate rise in coronary flow and a prompt return to normal on restoration of an oxygenated blood flow to the coronary circulation

Anoxia limited to the myocardium was also produced when the heart was temporarily stopped with the injection of a solution of potassium citrate into the ascending aorta occluded above the ostia of the coronary arteries The heart was maintained in asystole for a period of fifteen minutes Following release of the clamp on the aorta and restoration of the coronary circulation, there was a

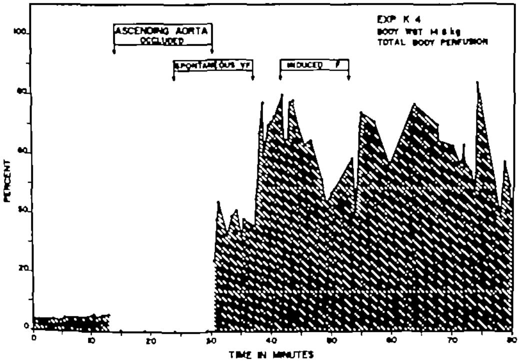


FIGURE 145

marked increase in coronary flow which persisted to a moderate degree for the duration of the perfusion (one hour) (Figures 146 and 147) In another experiment (Figure 148) there was a sharp fall in blood pressure and in both total and coronary flows after the clamp on the aorta was released. After a modest transfusion (170 cc) the blood pressure rose and the coronary and total flows increased markedly the former far above the control level Again in this experiment, the coronary arteriovenous oxygen difference decreased markedly coincident with the rise in coronary flow An elevated coronary flow in this experiment like the previous one persisted for at least one hour the duration of the perfusion

The Influence of Vasopressor Drugs on Coronary Flow As in the right heart by pass experiments there was a marked increase in coronary flow following the administration of arterenol A larger dose of the drug was required in the total by pass experiments to cause a rise in blood pressure and coronary flow presumably because of the dilution of the drug by the blood required to prime the oxygenator

The Influence of Ventricular Fibrillation on Coronary Flow When ventricular fibrillation was induced in the presence of rela

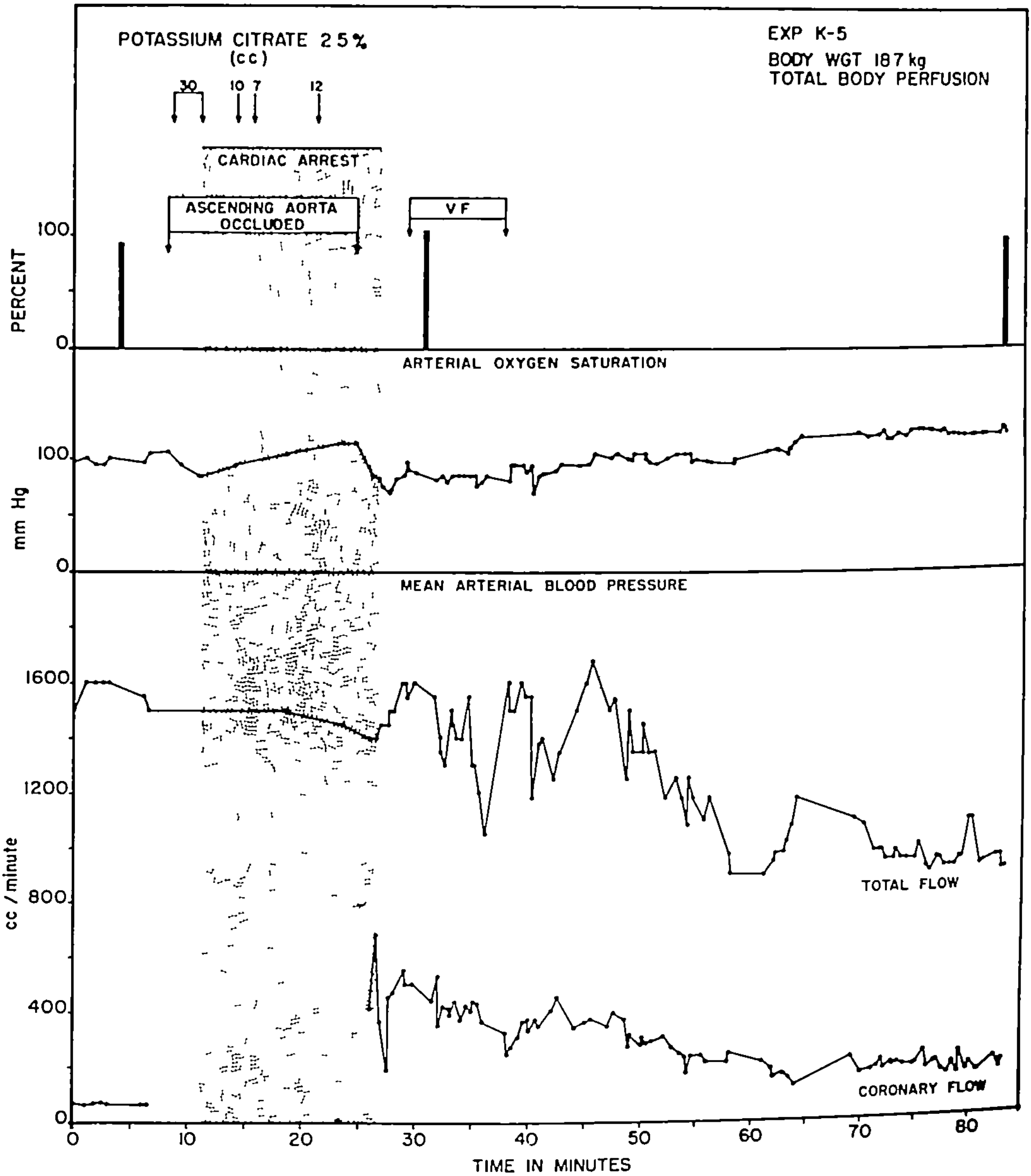


FIGURE 146

tively normal coronary flows there was usually but not invariably a rise in flow. When ventricular fibrillation occurred spontaneously or was induced in the presence of large coronary flows, no further increase in flow was observed. In some of these experiments there was a fall in blood pressure, total flow and coronary flow coincident with the onset of ventricular fibrillation.

DISCUSSION

Several factors have long been recognized as influencing coronary flow, and a detailed study of these factors has been made by

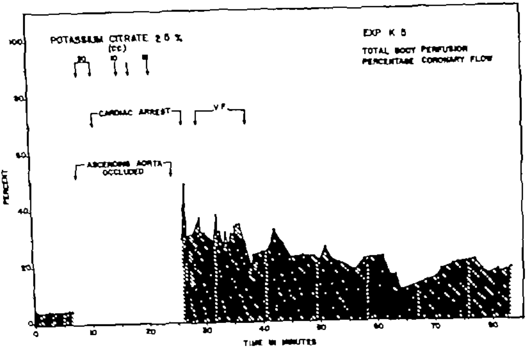


FIGURE 147

many physiologists A comprehensive contemporary study of the coronary circulation has been made by Gregg and Sabiston[11] Gregg summarizes the factors controlling coronary flow as follows "flow in either coronary artery will vary directly with the effective perfusion pressure head (aortic or central coronary pressure—right atrial pressure) and with the size or mean bore of the coronary bed The bore of the coronary bed is regulated to increase flow by changes in the intrinsic smooth muscle of the coronary vessels as mediated by nervous humoral and metabolic influences (active coronary dilatation) and by a passive or mechanical mechanism arising from myocardial contraction during systole (passive dilatation)"[11]

In addition to the above factors that will influence coronary flow during total body perfusion direct trauma to the coronary vessels during cardiac surgery and resuscitation may result in changes in coronary flow There is some evidence from experiments carried out thus far that cardiac manipulation and massage especially where the perfusion has been carried on for some time results in a dilatation of the coronary vessels and increased coronary flow

One remarkable fact about coronary flow is the enormous in

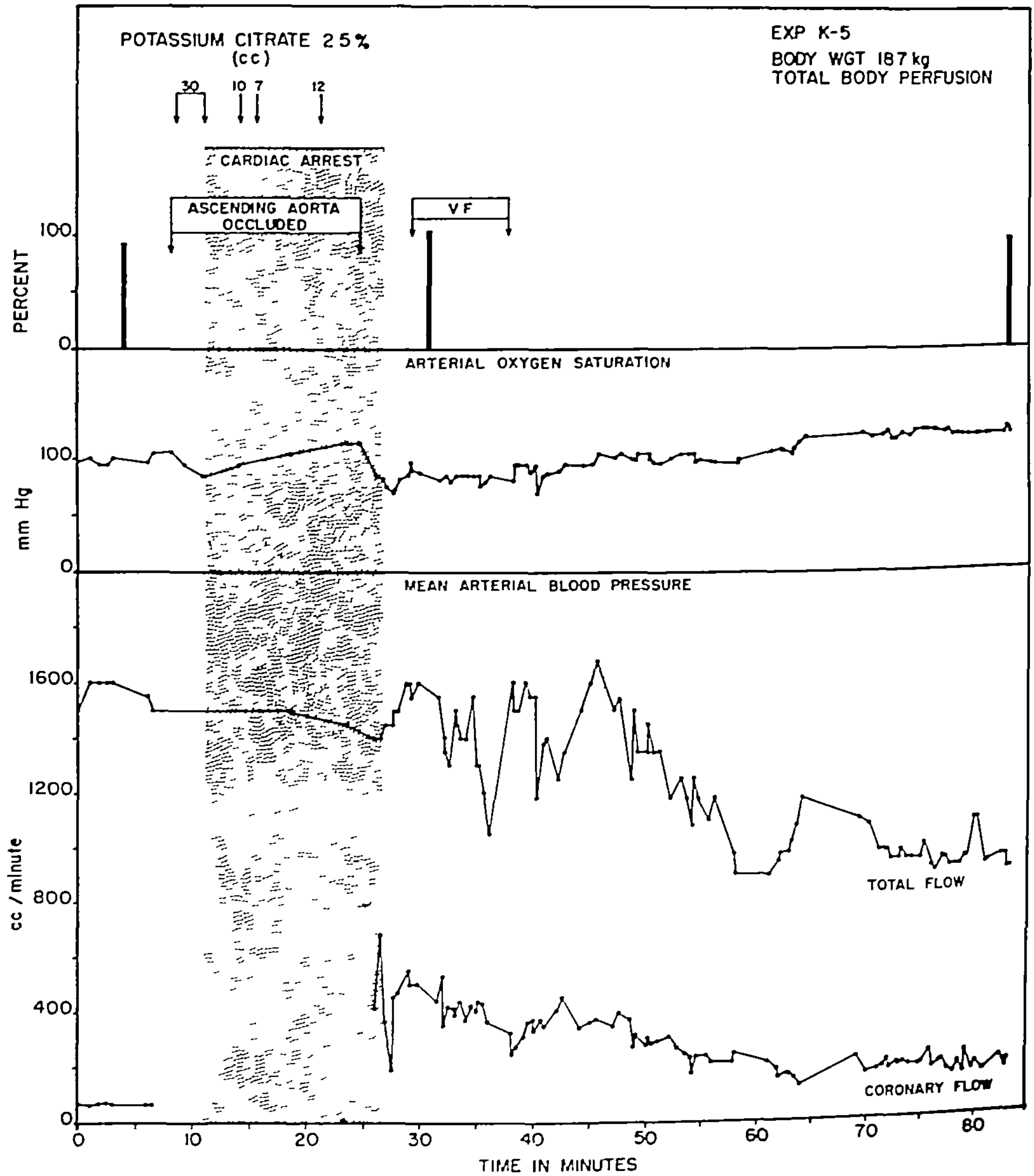


FIGURE 146

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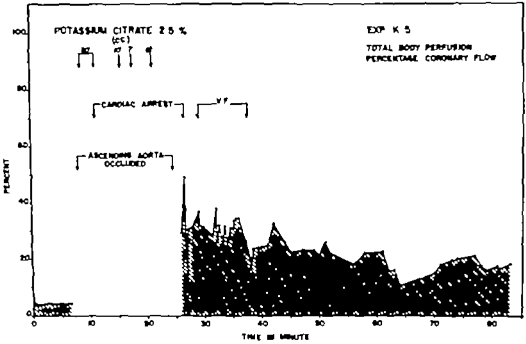


FIGURE 147

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One remarkable fact about coronary flow is the enormous in

crease that follows the development of hypoxia[2] As shown by Lord *et al*,[8] the flow usually returns promptly to normal if the period of hypoxia has not been prolonged From experiments performed thus far, it would appear that prolonged hypoxia or anoxia of the myocardium is followed by a delay in the return of the

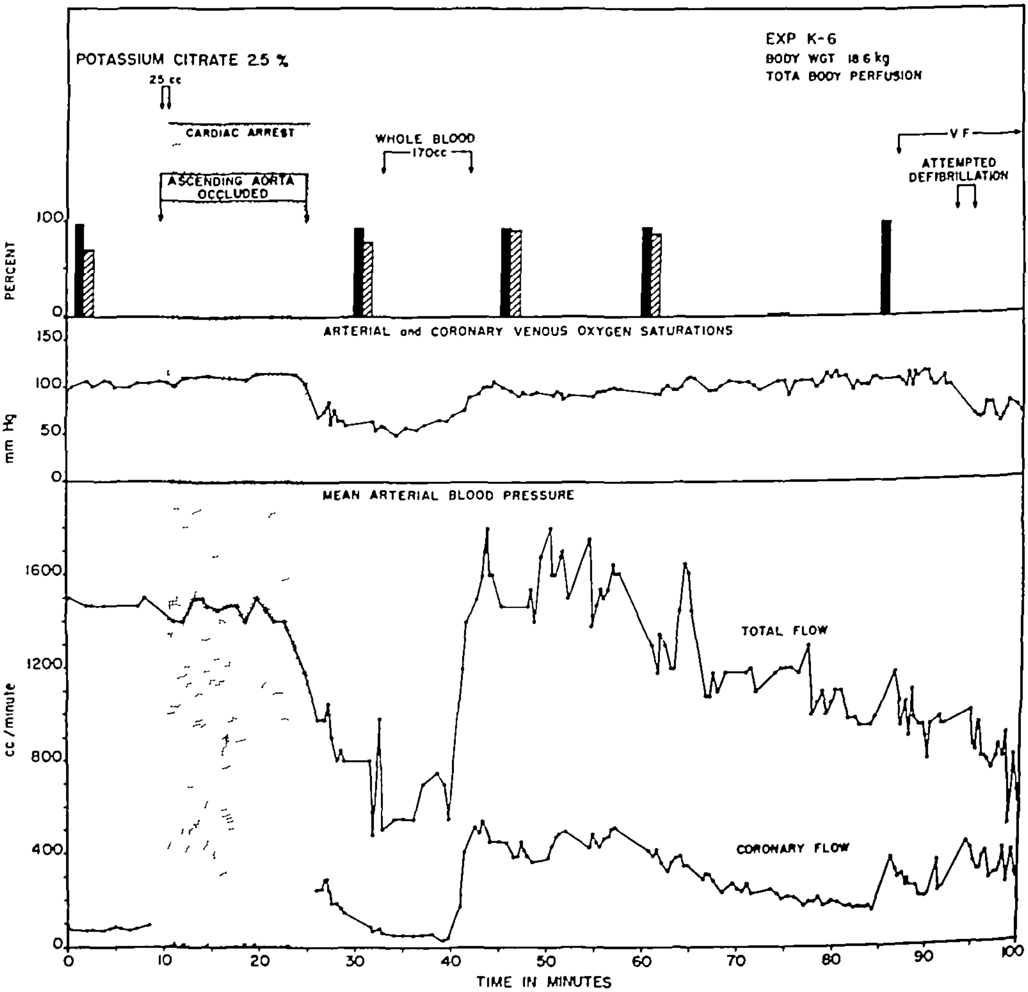


FIGURE 148

coronary flow to normal A constant finding with the increase in coronary flow following a period of anoxia and accompanying hypertension is the decrease in coronary A-V oxygen difference According to Gregg and Sabiston[11] this might be termed "benign dilatation" for the local oxygen demands do not exceed the increased oxygen supply The persistence of a decreased coronary A-V difference for about one hour after the relief from anoxia,

suggests the possibility of local changes in the coronary vessels that may be the direct result of the anoxia It will be of interest to continue these experiments and to prolong the period of anoxia These observations suggest that prolonged exposure of the coronary vessels to low oxygen tension may in some way damage the vessel walls at least temporarily Paul and associates[12] have demonstrated restoration of vigorous rapid fibrillation despite thirty to forty minutes of ventricular fibrillation with complete myocardial ischemia They believe that the anerobic metabolism of the cardiac glycogen "may be sufficient to sustain intact, for reasonable periods the labile enzyme system responsible for the generation of high energy phosphates" Successful defibrillation of the heart in their experiments was not always possible It is interesting in this regard that Weslowski and associates[11] were able to obtain long term survivors in only 21 per cent of dogs whose myocardia had been deprived of oxygen for thirty to sixty minutes during total body perfusion These investigators also noted a consistent fall in arterial blood pressure when the clamp occluding the aorta above the coronary ostia was released and again when the perfusion was discontinued. In the first instance they believe the fall in pressure might be due to a sudden flooding of a widely dilated coronary bed The fall in pressure following discontinuation of the perfusion was believed to be related to myocardial weakness secondary to the prolonged period of anoxia

Read, Johnson and Lillehei[17] have observed that coronary flow during total body perfusion is "remarkably liberal." They also noted that "when the total body flow is reduced or if perfusion is prolonged the proportion of blood passing through the myocardium increases favoring the heart over body organs" They found that the flow through the beating empty heart was essentially the same as that reported for the normally functioning heart The nearly identical control flow studies in the experiments with right heart by pass alone and with total heart by pass (Table I) would confirm these observations Read Johnson and Lillehei believe that "this extravagant perfusion" of the coronary circulation in the by passed heart accounts for the favorable response of this organ in the presence of low total body perfusions

Finally the widely open coronary vessels that follow a period

of anoxia secondary to occlusion of the ascending aorta may be a significant factor in the survival of the organism as a whole Following prolonged myocardial anoxia, a large proportion of the total cardiac output passes directly through the coronary circulation and may never reach other parts of the systemic circulation On the basis of the decreased coronary A-V oxygen difference, essentially a large A-V fistula is established in the coronary circulation and the peripheral arterial circulation is denied this amount of circulating blood volume Transfusion under these circumstances should be helpful, as noted empirically by Weslowski and associates,[13] provided the myocardium can function sufficiently well to maintain an effective perfusion pressure

Further experiments are in progress to test the validity of these early observations and postulates It is possible that the coronary circulation is not only of importance in the survival of the myocardium but directly and indirectly in the maintenance of the peripheral circulation Deliberate cardiac arrest for open heart surgery may be a safer technic provided the myocardium can be prevented from incurring an oxygen debt

SUMMARY

Experiments on coronary flow with partial and total body perfusion have been described The influence of factors previously known to effect coronary flow have been confirmed After the prolonged myocardial anoxia, produced by the occlusion of the ascending aorta, there is a prolonged period of vasodilation of the coronary vessels Following the release of the aortic occlusion, the temporary increase in coronary flow may be detrimental to the animal

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STUDIES IN CARBOHYDRATE METABOLISM OF THE ISOLATED DOG HEART WHILE BEATING AND DURING INDUCED ARREST[1]

By

JOHN E. JESSEPH, M.D.,[2] PAUL W. HERRON, M.D.,[2] LOREN C. WINTERSCHEID, M.D.,[2] ROY R. VETTO, M.D.,[3] *and* K. ALVIN MERENDINO, M.D.

ACCELERATING progress in any field of endeavor usually outstrips the basic knowledge available in that field. Characteristically, the current advances in intracardiac surgery have gone beyond complete understanding of basic physiology in some areas. Myocardial metabolism is one of these areas. Despite many apparently accurate appraisals of this metabolism *in situ* or in heart-lung preparations (Evans, 1939, Bing, 1951, 1953, 1954, Spencer, 1950, Gott, 1957, Goodale, 1953), unity of evidence is lacking with regard to the composition of this metabolism. The metabolism of the isolated, non-working or arrested heart as seen in the present era of cardiac surgery has little or no documentation.

Our interest in this area led us to devise an experimental preparation which would allow a precisely controlled study of the biochemical activities of the isolated, non-working heart while beating, during and following arrest.

From the Department of Surgery, University of Washington School of Medicine, Seattle 5, Washington.

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[2] U. S. Public Health Service Postdoctorate Research Fellow, National Heart Institute.

[3] Supported by Cardiovascular Training Grant HTS-5194.

METHODS

Two dogs were anesthetized with i v Nembutal and heparinized with 2 mg of heparin/kg of body weight The heart and great vessels of the donor animal were exposed via a bilateral thoracotomy A catheter was placed in the brachiocephalic artery so that the tip was neither against nor through the aortic valve Umbilical tapes were placed loosely about the cavae

The femoral artery and vein of the other dog (perfusing dog) were exposed and catheterized The femoral artery catheter was connected to the brachiocephalic artery catheter of the donor dog with a piece of Tygon tubing This tubing was passed through a Sigmamotor pump which controlled the rate of perfusion The femoral vein catheter was connected to a small chamber (defoaming chamber) which contained a coil of stainless steel wire coated with antifoam Figure 149 diagrams the cross perfusion preparation.

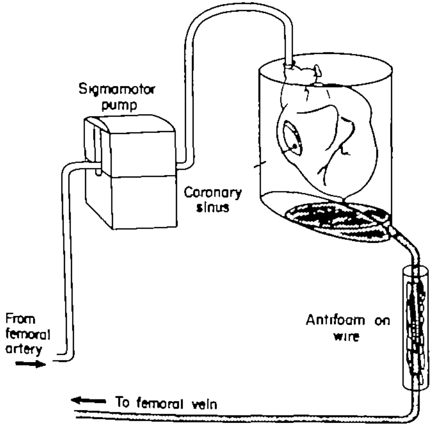


FIGURE 149

When the above preparations were complete, the cavae in the donor dog were occluded with the umbilical tapes The aorta was clamped distal to the brachiocephalic artery and perfusion begun The donor dog's heart was then excised and suspended in a large plastic chamber Venous blood, under gravity flow, returned to the perfusing dog via the defoaming chamber and femoral vein

Baseline measurements were carried out by drawing simultaneous paired arterial and coronary sinus blood samples at varying time intervals up to two hours These samples were analyzed as follows 1 pH (Beckman Model G pH meter), 2 hematocrit (Van Allen, 1925), 3 hemoglobin (Beckman B Spectrophotometer), 4 potassium (Perkin-Elmer flame photometer), 5 oxygen and carbon dioxide (a single Van Slyke gas analysis apparatus operated by one individual), 6 glucose (Reinhold, 1953), 7 pyruvic acid (Segal, Blair, and Wyngaarden, 1956), 8 lactic acid (Barker and Summerson, 1941)

In the determination of lactic acid (Barker and Summerson, 1941) it is very important to separate the protein-free solution from the precipitate by centrifugation followed by pipetting off the supernatant The protein precipitate can be separated from the supernatant by filtration However, the lactic acid present on one's hands will cause gross unpredictable errors in the determinations if the filter paper used for such a filtration is handled

Cardiac arrest was induced with approximately 15 ml of a solution containing 1 gram of potassium citrate in 25 ml of arterial blood After a constant time interval, perfusion was reinstituted and the first blood coming from the coronary sinus sampled The total utilization of the various metabolites during arrest was estimated by comparing this venous sample with an arterial sample obtained immediately prior to arrest During the postarrest, perfusion sampling was repeated as in the baseline studies At the end of each experiment the flow was measured and the hearts weighed, after the vessels were excised and all available fat trimmed

RESULTS

In our preparation the mean exchange of metabolites was as follows

TABLE I

	ml or mg /100 gm /min ± 95% Confidence Interval	Mols $\times$ 10^{-3}/100 gm /30 min
Oxygen uptake	3 8 ± 40	508 50
Carbon Dioxide output	3 3 ± 40	411 90
Glucose uptake	6 12 ± 1 45	101 40
Lactic acid uptake	11 ± 2.80	3 60
Pyruvic acid uptake	053 ± 1	1 68

When the A V concentrations of the various metabolites are plotted against time a group of points is seen that suggests a linear relationship These linear regressions of A V concentrations of the metabolites plotted against time are shown in Figure 150 The lines for glucose carbon dioxide oxygen and pyruvic acid closely approximate horizontal lines Indeed their slopes are not statistically different from the slope of a horizontal line It is therefore reasonable to assume that the exchange of these metabolites i.e oxygen, carbon dioxide glucose and pyruvic acid is proceeding at a relatively stable rate regardless of the perfusion time The mean uptake of pyruvic acid is so small that it does not differ significantly from zero This suggests that there is very little if any uptake of this metabolite in our preparation.

The line representing lactic acid exchange appears steep However its slope is not significantly different from that of a horizontal line The mean exchange of this metabolite has a wide confidence interval which reflects the wide variation of A V concentrations These wide variations were not related to time or the particular preparation Statistically therefore we conclude that the metabolic processes affecting lactic acid exchange are in a relative state of balance in our preparation Furthermore the mean value of the A V concentration of lactic acid is very small and not significantly different from zero This strongly suggests that lactic acid is neither primarily utilized nor excreted in our preparation

The mean exchange of metabolites in the heart arrested for 30 minutes is estimated as tabulated at the top of the next page We estimated the energy production in 30 minutes in the isolated perfused beating heart by calculating the total number of mols of glucose utilized aerobically and anaerobically These values were converted to calorie equivalents by multiplying by 680 calories

TABLE II

	ml or mg/100 gm/30 min ± 95% Confidence Interval	Mols $\times$ 10^{-5}/100 gm/30 min
Oxygen	04 ± 01	177
Carbon Dioxide	118 ± 02	525
Glucose	064 ± 03	036
Lactic Acid	266 ± 19	295
Pyruvic Acid	0018 ± 0018	0018

Exchange and Utilization of Metabolites in the Perfused Isolated Beating Dog's Heart

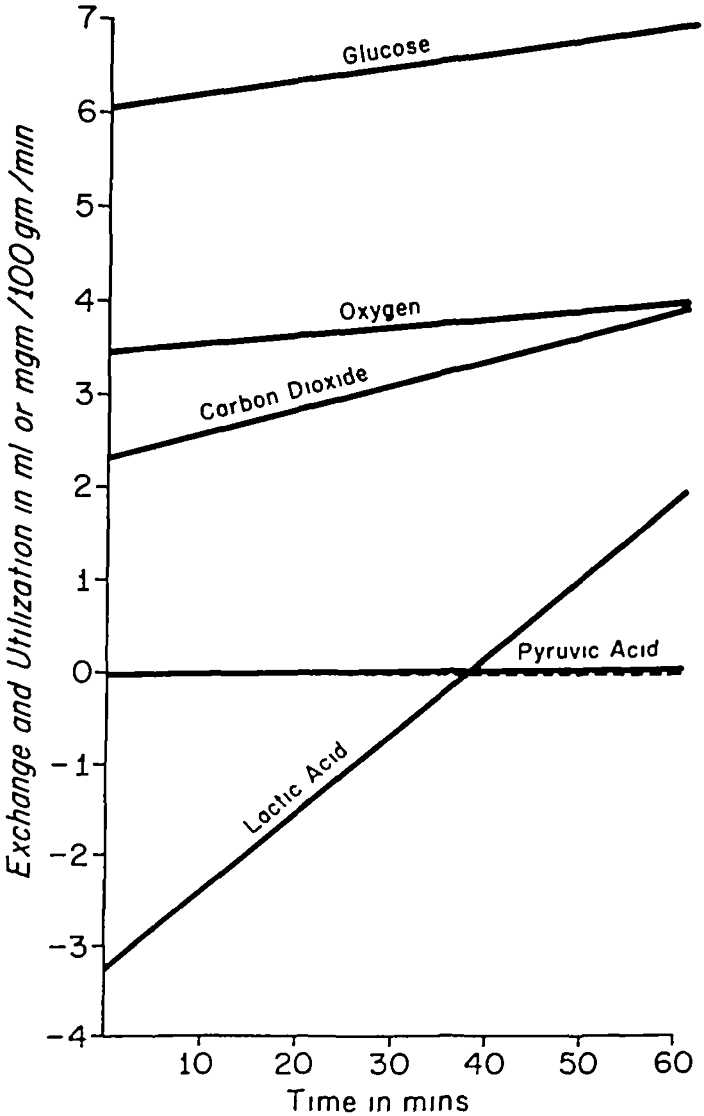


FIGURE 150

and 38 calories respectively.* A similar calculation was carried out for the metabolism during 30 minutes of induced arrest. A comparison of the estimates of energy production are shown in Table III.

A striking difference is apparent. Carbohydrate metabolism provided approximately 690 calories of energy in 30 mins. in the beating heart but only 0.3 calories in 30 mins. in the arrested heart. In other words, for identical periods of time the energy production of carbohydrate metabolism in the arrested heart is only 1/2000 of that in the beating heart.

Another difference between the beating and the arrested heart was found in the pH of the coronary sinus blood. In the beating heart the coronary sinus blood had a pH that averaged 7.35. The

TABLE III

AN ESTIMATION OF ENERGY PRODUCTION FROM CARBOHYDRATE METABOLISM IN THE ISOLATED DOG'S HEART DURING PERFUSION AND ARREST

Type of Metabolism	Perfused and Beating (30 min.)	Arrested (30 min.)
Aerobic	690 calories	2 calories
Anaerobic	1.4 calories	0.57 calories
Total	691.4 calories	2.57 calories

first sample of coronary sinus blood after arrest had an average pH of 7.00. It is not difficult to imagine the ill effects such an acidosis could have on cellular integrity.

DISCUSSION

Throughout the literature on myocardial metabolism, reference

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*One mol of glucose metabolized aerobically contributes an estimated 670-680 Calories of energy. When metabolized anaerobically, a mol of glucose contributes 36-38 Calories. A Calorie (large calorie) is equivalent to 1000 calories.

is made to two features which serve to differentiate it from skeletal muscle metabolism First, not only glucose but also lactic acid serves as a substrate for oxidative carbohydrate metabolism The quantity that lactic acid contributes to the total energy production is variously estimated at 30-100% Table IV summarizes various estimates of the utilization of glucose and lactic acid and their contribution to the carbohydrate energy production of the myocardium We are unable to confirm the utilization of lactic acid by the myocardium in the experimental preparation herein described

Second, it is frequently stated that the uptake of glucose and

TABLE IV

Author	Method	Glucose Utilization		Lactic acid Utilization		Estimated Total Energy		Measured Work
		Mg /100 gm./min	calories	Mg./100 gm./min.	calories	calories	Kg meters	Kg. meters
McGinty and Miller - 1933	Isolated perfused beating dog's heart	33	1 4	2 5	9 3	10 7	4 57	not given
Present Study 1957	"	6 12	23	11	4	23 4	10 0	Not measured
Goodale and Hackel -1953	Beating anesthetized dogs heart *in situ*	5 8	21 9	4 6	17 3	39 2	16 74	not given
Edwards et al 1954	"	4 3	17	7 9	29 8	46 8	19 98	not given
Gott et al 1957		3 7	14	2 5	9 4	23 4	10 0	not given
Evans 1939	Heart - Oxygenator Preparation	1 2	4 6	3 3	12 4	17 0	7 26	2 72
Bing et al 1953	Human *In vivo*	6 23	24	2 87	11	35	14 94	5 25

lactic acid by the myocardium in a constant working state is a function of the arterial concentration of these compounds This suggests that the myocardium is acting as an "end-organ" to two constantly changing common whole blood components, rather than depending on its own needs for the complete regulation of this utilization The correlation coefficients for glucose and lactic acid extractions against their arterial concentrations were calculated for our baseline studies A t test of these correlation coefficients demonstrated that they were not significant * Thus, our

* (Glucose, r = 2068, t = 1 1192, n = 13, 1 < 2P < 2 Lactic acid, r = 103 t = 5863, n = 32, 6 < 2P < 5)

preparation shows no correlation between utilization of glucose and lactic acid and their arterial concentrations This is in agreement with McCinty and Miller (1933) who were also unable to find any correlation between glucose and lactic acid uptake and their arterial concentrations Our investigation into the parameters of induced cardiac arrest is only beginning As could be predicted the energy production of an arrested heart must be very small Such a heart can metabolize some carbohydrate on the small amount of available oxygen but it must also depend on the very low energy producing anaerobic carbohydrate metabolism It was not anticipated that the values of energy production in the arrested heart would be only 1/2000 of that in the beating heart The magnitude of this reduction was not anticipated to be so great Further investigation of the post arrest perfusion may elucidate some "wash-out" of lactic acid that accumulated during the arrest This would tend to increase slightly the estimation of caloric production from the anaerobic system during arrest but would not alter greatly the magnitude of the differences between the beating and arrested hearts

The marked fall in the pH of the blood resting in the coronary circulation during arrest is also surprising This certainly suggests that the suspension of the arresting compound in a buffer solution might serve to circumvent this marked acidosis and prevent myocardial cellular damage

CONCLUSIONS

1 The carbohydrate metabolism of the isolated, perfused beating heart as described herein is proceeding at a relatively steady rate and glucose serves as the primary substrate for this metabolism

2 No correlation between glucose or lactic acid uptake and their arterial concentrations could be found.

3 The arrested heart produces approximately 1/2000 as much energy from carbohydrate metabolism in a standard interval of time as is produced by the perfused beating heart

4 The pH in the circulatory bed of the heart arrested for 30 mins falls to levels of 7 00

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CARDIAC METABOLISM IN INDUCED ARREST

By

HUGH H BENTALL, F R C S

IN JULY 1955 Dr Melrose and his team at the Postgraduate Medical School of London advocated the use of potassium citrate for inducing elective cardiac arrest. We believed that the energy requirements of the resting heart would be only a very small proportion of its energy needs whilst beating and that coronary flow could therefore be safely occluded for limited periods of time and from our early experiments we concluded that at least fifteen minutes was safe This premise as a great many of you know from experience has proved correct and we have used the method clinically as a routine The obvious question on which we had little evidence was the safe maximum period of arrest with full and permanent recovery In order to investigate this and also to shed light on the behavior of cardiac muscle when rendered anoxic in this way we have used several different and to some extent complementary methods

The hearts of some seventy rabbits were perfused by the well known Martin Langendorff technique and arrested for varying periods of time in most cases repeatedly In a number of experiments the pulmonary artery of the isolated heart was cannulated and the effluent representing the entire coronary flow was collected and determinations of the pH and lactate content made before and after known periods of arrest. In another series of experiments intact dogs were used, the aorta and coronary sinus being cannulated directly at operation The lactate content of the aortic blood was compared with that in the coronary sinus effluent both whilst the heart was beating and while it was being perfused after known periods of arrest I shall deal first with the results obtained in the isolated heart In all our work with this technique great care was taken in the design of the apparatus that the heart

should be kept at a known constant temperature The particular arrangement which we use has been described by one of our collaborators, Dr Baker of Charing Cross Hospital Medical School, London In order to provide some figures by which the recovery of these hearts could be assessed we compared the amplitude of the ventricular contraction before the arrest with that obtaining within fifteen minutes of the end of each experimental period

After fifteen minutes arrest with potassium citrate at 37°C, recovery was between 98% and 100% in most hearts After thirty minutes of potassium citrate arrest at 37°C, similar results were obtained This contrasts quite strikingly with the results of simple occlusion of coronary flow without prior arrest with potassium citrate, after fifteen minutes, recoveries were between 76% and 96%, whereas after thirty minutes the best was 76% and most below 20% After forty minutes or more of potassium citrate arrest, recoveries were between 10% and 70% but most were of the order of 40% It will of course be appreciated that these results are of rabbits' hearts beating only on oxygenated Locke's solution (A fuller description of this work has been published elsewhere, Baker *et al*, 1957) The next logical step was to determine the oxygen requirement of the arrested heart This, however, is not a very satisfactory procedure for while it is arrested without coronary flow direct chemical methods cannot be used, and if one adopts the alternative of maintaining the heart arrested with a minimum concentration of potassium citrate in a continuous perfusion one is altering the conditions of the experiment We have therefore sought evidence from lactate determinations on the coronary effluent immediately after the perfusion is resumed following periods of coronary occlusion, and one can compare results obtained with and without prior arrest with potassium citrate (Figure 151) Here the increase in lactic acid concentration in the first ml of effluent received from the heart after resumption of coronary flow is plotted against the time for which the coronary flow was interrupted The line on the left shows the differences obtained in hearts allowed to beat without coronary flow and on the right with prior arrest by potassium citrate It will be seen that the same concentration of lactic acid is attained after five minutes'

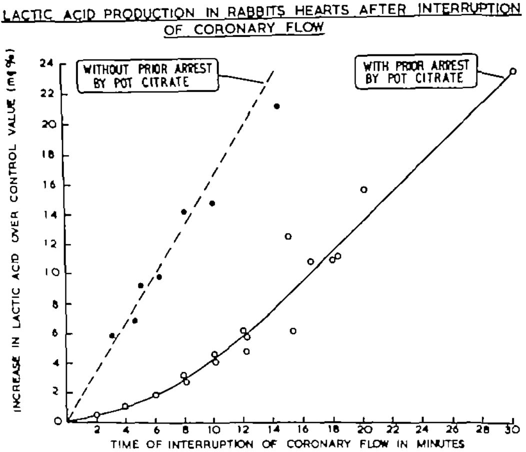


FIGURE 151

coronary occlusion without prior arrest as after fifteen minutes with prior arrest. This indeed, is the sort of change which one would expect. In the absence of coronary flow the heart is respiring purely anaerobically that is to say the energy is derived principally from glycolysis as far as lactic acid The surprising thing is the extent of anaerobic glycolysis in the absence of any obvious work done or put into biological terms the energy necessary for the prevention of entropy is considerable and may represent as much as one third of the requirements during beating This capacity of the heart for anaerobic respiration seems to be a relatively new concept amongst biologists but can of course be inferred from the very fact that hearts can recover after induced arrest without coronary flow even without the demonstration of an increase in lactic acid formation That these results are not due to any chemical effect of the potassium citrate is demon

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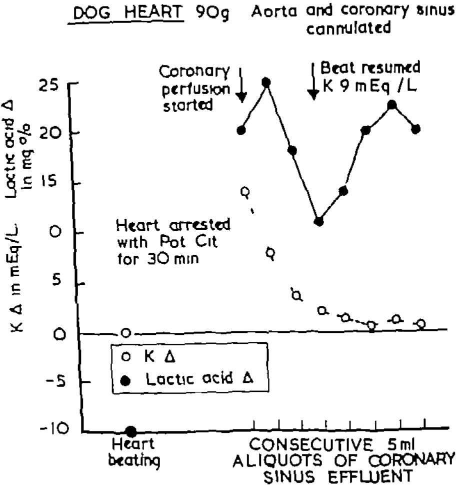


FIGURE 153

will be noticed that there is no difference in the potassium level between the aortic blood and the coronary sinus blood When coronary sinus perfusion is started the potassium level falls rapidly and in this dog s heart after only 20 ml. had passed through the coronary sinus the heart began to beat At this point the lactate which had started to fall then promptly began to rise again although the potassium continued to fall until a normal level was reached A similar result is seen in the next figure (Figure 154) in which the dog s heart has been arrested for forty five minutes but in this instance the beat was not resumed immediately the potassium fell to a level at which a beat should be possible This effect has been observed in other experiments but the cause for this is not clear This work is continuing and a more elaborate biochemical investigation is planned We would like very much to perform

LACTIC ACID PRODUCTION IN THE ARRESTED HEART WITH CONTINUOUS PERFUSION (1)

DURATION OF ARREST IN MIN	CONTROL VALUE	OBSERVED VALUE	DIFFERENCE
8	2 6	2 3	-0 3
15	2 3	2 6	0 3
20	5 7	3 7(3)	2 0

(1) PERFUSION WITH LOCKE'S SOLUTION CONTAINING POT CITRATE 2 5 mg /ml

(2) LACTIC ACID LEVELS EXPRESSED AS mg %

(3) AFTER 10 MINUTES OF NORMAL BEATING LEVEL WAS 5 2

FIGURE 152

strated in the next figure (Figure 152) in which it is seen that if the heart is held arrested with a continuous perfusion with Locke's solution containing potassium citrate at a concentration of 2 5 mg /ml it is seen that for the short periods of arrest there is no significant difference between the observed and the control value and when it is prolonged for twenty minutes then the initial control value is higher than the observed value

In the anesthetized, intact animal control samples were taken from the aorta and from the coronary sinus with the heart beating normally The heart was then arrested in the normal manner with potassium citrate in blood and at the conclusion of the experimental period of arrest the coronary effluent was collected into 5 ml aliquots and each aliquot was estimated for potassium and for lactate In Figure 153 is shown a representative experiment with the heart arrested for thirty min It will be observed that the control values for the heart beating show 10 mg % less lactic acid in the coronary effluent than in the aorta That is to say, the heart is extracting lactate from the circulating blood and using it for energy production This has already been observed by Bing in his classical experiments in coronary sinus cannulation in man It

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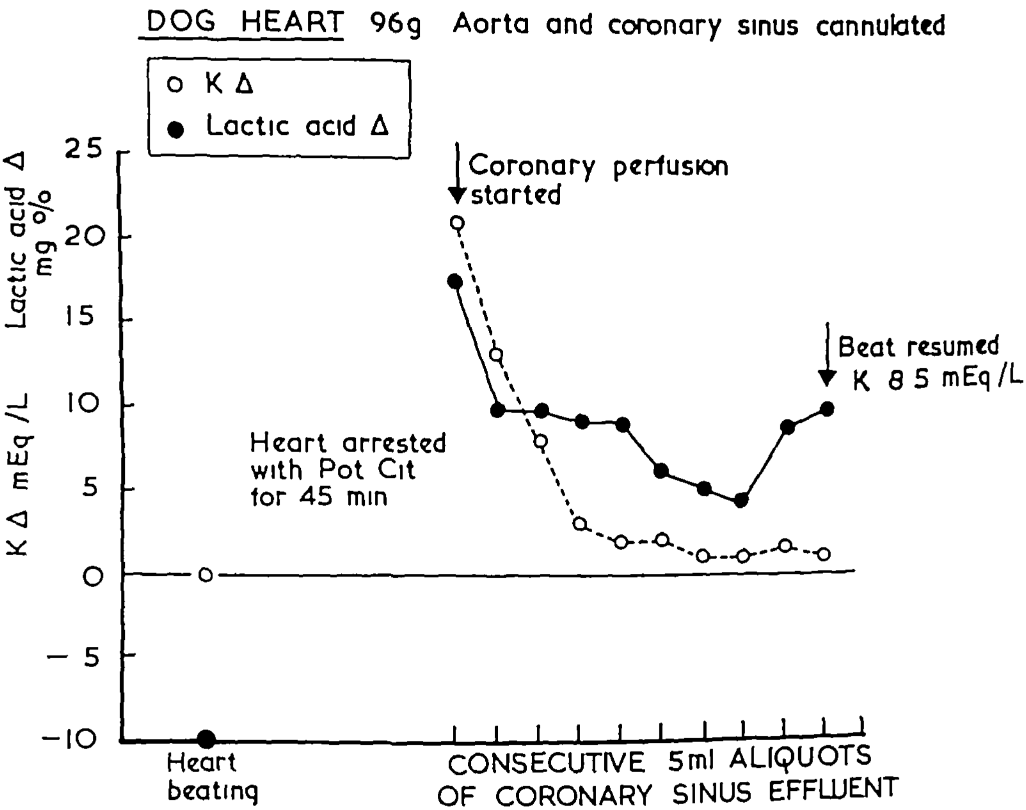


FIGURE 154

similar determinations in man during operations on the right side of the heart but we have not yet felt justified in taking the additional time involved

To sum up then, during induced cardiac arrest the heart is maintained intact by anaerobic glycolysis leading to the formation of lactic acid with the production of a local acidosis It is obviously desirable that the glycogen stores in the heart should be adequate and indeed a small contribution to a higher carbohydrate substrate perhaps could be achieved by adding glucose to the blood used for stopping the heart, but it is doubtful whether the buffering power of normal blood and tissue could be much improved by the addition of more bicarbonate Of one thing I am certain, and that is that there is no fixed safe period of arrest It must vary according to the condition of the heart at the time when it is arrested, but it is probably true to say that periods in excess of thirty minutes in patients who have been in heart failure will carry an appreciable mortality

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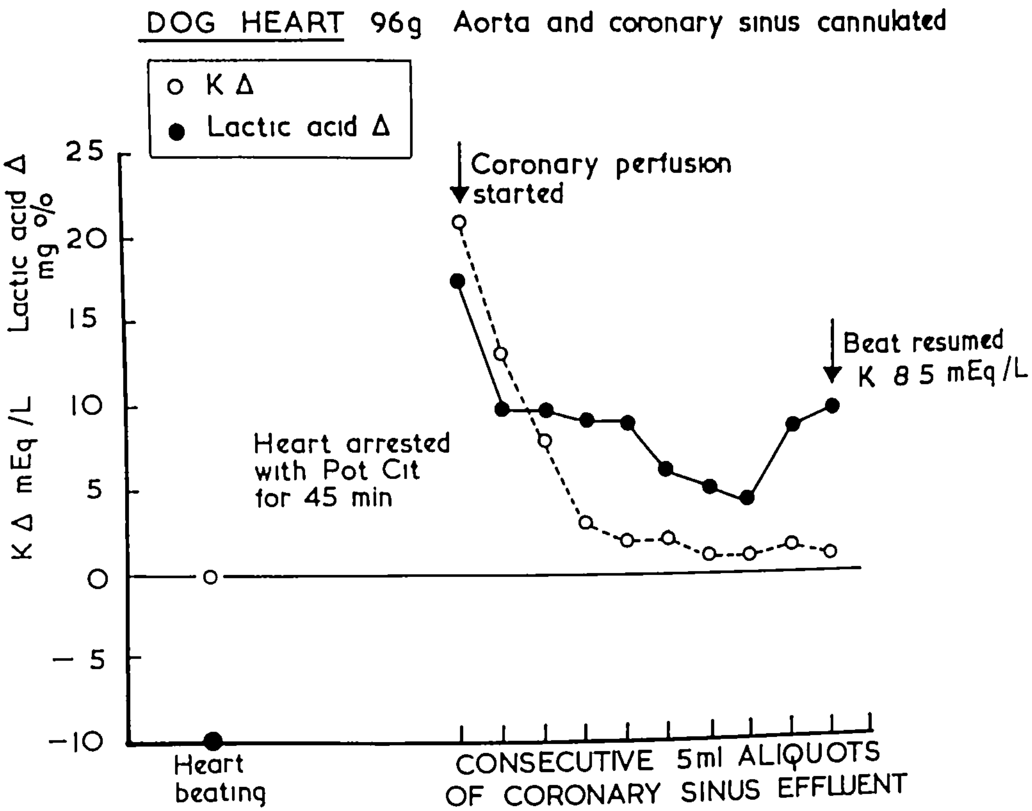


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poses 1) to observe any biochemical deviations in the blood from normal and 2) to observe the water and electrolyte exchange between the myocardium and serum following use of the bubble oxygenator perfusion and elective cardiac arrest

PROCEDURES AND CALCULATIONS

Young adult, healthy, mongrel dogs were used Prior to surgery 30 mg morphine sulfate were given followed by light anesthesia using intravenous sodium pentothal with a closed circuit McKesson system manual bag compression with a carbon dioxide absorbent (soda lime) and a cuffed tracheal tube Lead II electrocardiogram and femoral artery pressures were recorded throughout Routine right thoracotomy was performed and after preparation of the vessels 1 5 mg/kg body weight of heparin were given Venous catheters were inserted to the superior vena cava via the azygos vein and to the inferior cava via the right atrial appendage The arterial infusion catheter was placed in a carotid artery Venous occlusion and arterial perfusion were started at the same time After a short wait to be certain of an oxygenated, normally contracting heart an adequate peripheral pressure and a stable functioning pump-oxygenator the heart was arrested by infusing proximal to the cross clamped aorta a solution containing heparinized whole blood and potassium citrate (1 ml of 25% potassium citrate with 9 ml blood) using an amount in slight excess of that required to stop ventricular activity (usually 15-20 ml.) After a selected period of arrest the right atrium was opened and the aortic clamp removed After 200-300 ml of blood had been perfused through the heart and removed and discarded from the right atrium the atrium was closed with a clamp and the animal taken off the oxygenator as soon as heart activity was normal Protamine sulfate was then infused slowly intravenously and after a suitable waiting period the experiment was concluded. Any variables will be noted in the individual animal protocols

EXPERIMENTAL PROTOCOLS

Dog M10 Perfusion time—thirty-one minutes Arrest time—thirteen minutes Removal of heart—thirty nine minutes later

BIOCHEMICAL STUDIES OF THE MYOCARDIUM AFTER PERFUSION AND ARREST

By

PETER V. MOULDER, M.D., LILLIAN EICHELBERGER, PH.D., MICHAEL ROMA, GEORGE R. DAICOFF, M.D., *and* NORMAN SIDERIUS, M.D.

THROUGHOUT the period of development of pump-oxygenators for cardiac by-pass, acid-base studies have been essential in order to determine the effective but not excessive removal of carbon dioxide from the blood [1] Other acid-base studies have been correlated to the type of cardiac by-pass and the unit quantity of blood flow [2]

Only a few values on serum electrolytes have been presented thus far and little evidence of any disturbance indicated [3] Furthermore, no myocardial water and electrolyte changes between the plasma and heart muscle have been noted

For the requested purposes of this symposium, this experimental study obtained data on the bubble oxygenator perfused heart undergoing a period of elective cardiac arrest (potassium citrate) and a short recovery period Since the chemical characterization of the normal dog myocardium has been shown to have a small deviating set of values,[4] they are useful for comparing with experimental subjects, such as these In addition, we have found that the myocardium of animals subjected to total body hypothermia (22-25°) is essentially normal under such scrutiny [5] It is regrettable that the analyses of hearts undergoing simple perfusion cannot be included here for comparison The experiments to be presented were undertaken for the following pur-

From the Departments of Surgery and Biochemistry of the University of Chicago

This investigation was supported in part by a grant from the Home for Destitute Crippled Children and by a research grant (H2938) from the National Heart Institute of the National Institutes of Health, Public Health Service

collected in 500 ml bottles containing 20 mg heparin in 20 ml of 154 mM saline After anesthesia was established and prior to thoracotomy, the first blood sample was taken and at conclusion of the experiment another sample was taken from the femoral artery and the heart then quickly removed All blood samples were taken under oil for serum analyses Blood was defibrinated for whole blood analyses and hematocrit determinations The heart was treated as previously described[1] except that the dried powdered tissue[7] was used for all analyses instead of wet minced tissue The following determinations were made on the serum pH total CO_2 water chloride sodium potassium calcium magnesium and total nitrogen on whole blood cell volume water chloride sodium and potassium and on heart muscle water fat residual blood chloride sodium potassium calcium magnesium total nitrogen and collagen nitrogen All tissue analyses were calculated on a fat free blood free basis The chemical methods for all the analyses were enumerated in previous papers[1,8,9] Determination of the residual volume of blood afforded correction for the amount of constituents in the circulating blood left in the heart at the time of removal Since whole blood magnesium values were not determined the values were assumed from previous data[10] and used in the calculations for dogs M12 and M13 which had unusually large volumes of residual blood

Heart tissue is considered as having an extracellular compartment (F) consisting of connective tissue solids $(F)_s$ and extracellular fluid $(F)_U$ and an intracellular compartment (C) consisting of protein solids $(C)_s$ and water $(H_2O)_C$. In one kilogram of heart tissue the mass of the extracellular fluid was calculated from the chloride values[11] the connective tissue weight was estimated from the collagen nitrogen values and the intracellular segments deduced by difference from the total determined myocardial water and solids The calculations for the ionic concentrations in the fluids and fibers are given in detail in the presentation of normal myocardium[1] Parentheses ( ) represent milliequivalents or grams per kilogram of tissue brackets [ ] milliequivalents or grams per kilogram of water and braces { } represent milliequivalents or grams per kilogram of phase

Perfusion rate—54 ml/kg body weight/minute Remarks· After restarting the heart, ventricular tachycardia and then fibrillation ensued which required a single electric shock for defibrillation There was some blood loss from the aorta requiring some blood infusion after the cardiac procedure was completed At the time of removal, the heart appeared normal with a sinus rhythm and producing a normal systemic blood pressure

Dog M11: Perfusion time—twenty-five minutes, Arrest time—fourteen minutes, Removal of heart—twenty-eight minutes later, Perfusion rate—52 ml/kg body weight/minute Remarks After completion of the wash perfusion following arrest, the heart had to be compressed about five times as it increased strength of contraction

Dog M12: Perfusion time—thirty-two minutes, Arrest time—eighteen minutes, Removal of heart—forty-one minutes later, Perfusion rate—55 ml/kg body weight/minute Remarks Defibrillation with single shock was required after resuscitation in this dog as in M10

Dog M13· Perfusion time—twenty-four minutes, Arrest time—eighteen minutes, Removal of heart—twenty minutes later, Perfusion rate—50 ml/kg body weight/minute Remarks After the heart had been washed and the heart restarted a normal rhythm could not be obtained and the heart had to be aided by manual compression Although many contractions were effective, the heart continued to deteriorate and the left ventricle went into rigor although the right ventricle continued to have effective systole With the opportunity for differential study of a ventricle in rigor and one in apparently normal systole, the experiment was concluded The right ventricle was removed separately from the left and major portion of the septum, so that distinct analyses could be performed

The pump-oxygenator was the DeWall type with Sigmamotor finger pump [6] Stainless steel adaptors, Mayon plastic tubing, gum rubber tubing, perforated steel oxygen plate, a double set of Abbott stainless steel mesh filters and Dow Antifoam A Spray were used The oxygenator was not sterilized prior to use

Donor blood was obtained from two to four mongrel dogs and

collected in 500 ml bottles containing 20 mg heparin in 20 ml of 154 mM saline After anesthesia was established and prior to thoracotomy the first blood sample was taken and at conclusion of the experiment another sample was taken from the femoral artery and the heart then quickly removed All blood samples were taken under oil for serum analyses Blood was defibrinated for whole blood analyses and hematocrit determinations The heart was treated as previously described[4] except that the dried powdered tissue[7] was used for all analyses instead of wet minced tissue The following determinations were made on the serum pH total CO_2 water chloride sodium potassium calcium magnesium and total nitrogen on whole blood cell volume water chloride sodium and potassium and on heart muscle water fat residual blood, chloride sodium potassium calcium magnesium total nitrogen and collagen nitrogen All tissue analyses were calculated on a fat free blood free basis The chemical methods for all the analyses were enumerated in previous papers[4,8,9] Determination of the residual volume of blood afforded correction for the amount of constituents in the circulating blood left in the heart at the time of removal Since whole blood magnesium values were not determined, the values were assumed from previous data[10] and used in the calculations for dogs M12 and M13 which had unusually large volumes of residual blood

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TABLE I

ORIGINAL DATA SERUM, BLOOD AND HEART*

	Water Gm	*Cl m eq*	*Na m eq*	*K m eq*	*Ca m eq*	*Mg m eq*	*Total N m eq*	*Collagen N m eq*	*pH units*	*Total CO_2 m M*	*Fat %*	*Tissue Blood ml*	*Hematocrit %*
M 10													
Control Serum	924.7	113.1	147.1	4.31	4.70	2.01	8.69		7.33	25.9			
Control Blood	781.3	88.0	125.4	5.38									49.6
Final Serum	925.5	120.4	148.5	3.79	4.75	2.06	8.65		7.23	13.6			
Final Blood	810.5	96.2	127.5	5.53									41.2
Heart	803.2	35.26	42.29	81.05	2.32	15.04	27.0	5.41			1.90	27.1	
M 11													
Control Serum	924.9	114.4	149.2	4.20	4.86	1.87	9.19		7.45	22.5			
Control Blood	807.0	87.3	122.8	5.74									46.2
Donor Serum	924.4	123.6	142.3	5.14			9.43						
Donor Blood	807.0	89.8	116.4	6.21									40.4
Final Serum	929.7	124.8	147.8	3.87	4.84	1.91	8.00		7.30	15.9			
Final Blood	794.3	99.0	121.8	4.70									47.0
Heart	801.5	38.30	48.85	77.08	2.70	13.82	27.5	5.14			1.66	24.3	
M 12													
Control Serum	929.7	117.8	148.7	4.66	5.20	2.09	7.98		7.10	24.9			
Control Blood	783.0	87.5	118.7	4.88									49.2
Donor Serum	927.3	124.9	143.8	5.12			8.61						
Donor Blood	785.7	86.3	111.6	5.23									50.4
Final Serum	919.2	120.6	147.8	3.49	5.17	2.25	9.56		7.13	18.9			
Final Blood	751.0	83.7	113.6	4.99									63.0
Heart	814.0	63.0	85.4	51.6	6.25	11.31	25.8	4.84			2.10	19.2	
M 13													
Control Serum	919.0	123.7	147.0	4.47	4.93	2.16	9.90		7.21	21.0			
Control Blood	783.3	93.7	132.9	5.74									46.0
Final Serum	921.3	122.1	147.8	4.98	4.26	2.28	9.36		7.24	12.2			
Final Blood	799.4	96.7	134.2	6.90									43.3
Heart													
Left Ventricle	812.9	70.5	90.9	38.9	6.72	13.48	26.1	5.26			1.88	79	
Right Ventricle	811.7	49.6	61.3	62.7	3.52	18.27	27.2	5.08			3.02	77	

* Units are expressed per kilogram of blood free, fat free tissue

TABLE II

DISTRIBUTION OF WATER AND ELECTROLYTES BETWEEN SERUM AND RED BLOOD CELLS

	%	H_2O gm	Cl mEq	Na mEq	K mEq
M 10					
Control Serum	50 4	924 7	113 1	147 1	4 91
Final Serum	58 8	9 5 5	120 4	148 5	3 70
Control Cell	49 6	635 7	62 5	103 4	6 47
Final Cells	41 2	640 4	61 7	97 6	8 00
M 11					
Control Serum	53 8	924 0	114 4	149 2	4 20
Donor Serum	59 6	9 4 4	123 6	142 3	5 14
Final Serum	53 0	920 7	124 8	147 8	3 87
Control Cells	46 2	600 6	47 8	92 0	7 53
Donor Cells	40 4	633 0	50 0	78 2	7 80
Final Cells	47 0	641 [illegible]	70 0	9 6	5 64
M 12					
Control Serum	50 8	934 8	117 8	148 7	4 06
Donor Serum	40 6	927 3	124 9	143 8	5 12
Final Serum	37 0	919 2	120 0	147 8	3 49
Control Cells	49 2	631 5	50 3	87 8	5 10
Donor Cells	50 4	640 2	48 2	80 0	5 34
Final Cells	63 0	634 2	62 1	93 5	6 87
M 13					
Control Serum	53 4	919 0	123 7	147 0	4 47
Final Serum	56 7	921 3	122 1	147 8	4 98
Control Cells	46 6	628 0	50 2	116 7	7 10
Final Cells	43 3	639 7	63 5	116 4	9 42

Units are expressed per kilogram of tissue or fluid

RESULTS

The original data for serum, whole blood and heart muscle are given in Table I the serum and calculated red cell constituents are recorded in Table II When the final experimental values are compared with the control values it will be noted that the serum and cell water remained relatively constant Likewise the sodium, potassium, calcium and magnesium concentrations remained un-changed Although the cell volume of Dog M12 increased from a value of 49 per cent to 63 per cent during the experimental period the concentrations of the blood constituents were not significantly different The low serum pH and bicarbonate along with the high chloride values indicate a metabolic acidosis Fig

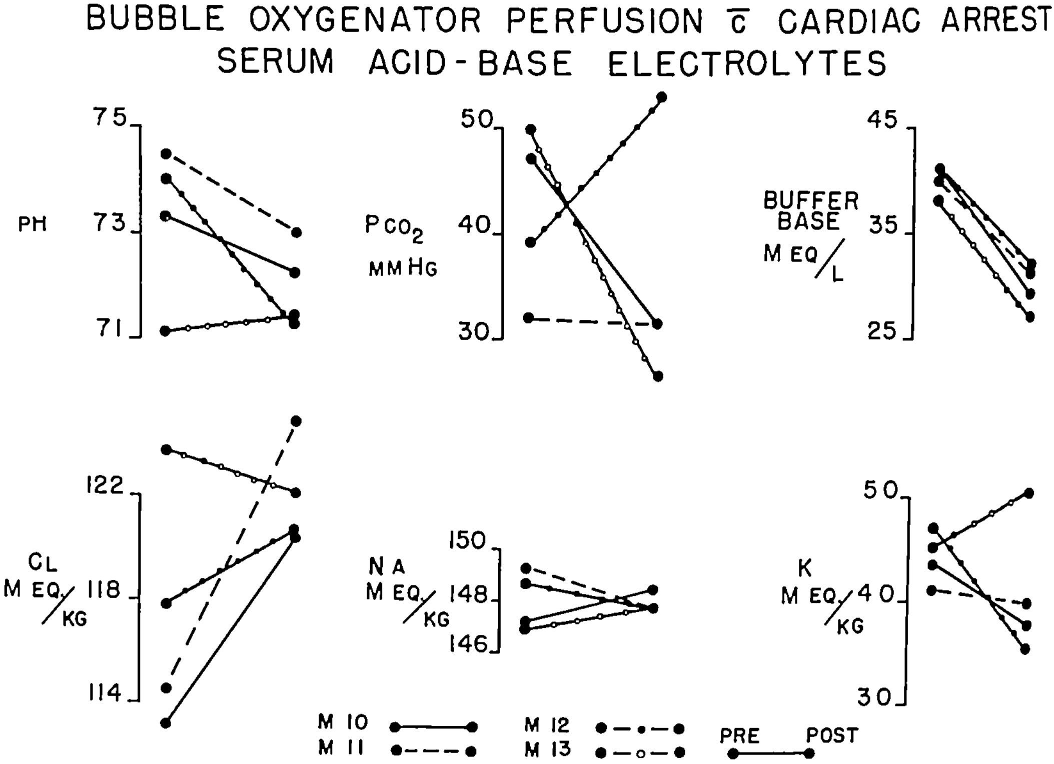


FIG 155 Serum acid-base and electrolyte data on dogs perfused with bubble type oxygenator and having elective cardiac arrest with potassium citrate The low pH and buffer base indicate a metabolic acidosis The high fixed acid anion, chloride, corroborates this finding Dog M13 started the procedure (after anesthesia) in metabolic acidosis The elevated final pCO_2 for serum of M12 indicates inadequate ventilation

ure 155 graphically represents the calculated acid-base data along with the buffer base quantities read from the Singer-Hastings nomogram [12] Although the majority of the animals attempted to compensate for the metabolic acidosis, Dog M12 had an elevated pCO_2 indicating poor respiratory compensation as a result of inadequate ventilation The donor bloods used in all of these experiments were not protected from CO_2 loss before the perfusion was begun When the experimental myocardial data are compared with those from a control series,[1] the following observations can be made In Dogs M10 and M11 the concentrations of constituents per kilogram of fat-free blood-free myocardium are not different from the control values In Dogs M12 and M13, however, there are many definite deviations and irregularities from the controls As indicated above, the heart of Dog M13 was

divided into right and left ventricles and analyzed separately. For some reason the heart muscle of Dog M12 and the left ventricle of M13 both showed an elevation of the total water content and significant increases in chloride, sodium and calcium values accompanied by marked decreases in potassium content. The right ventricular myocardium had a similar water content although a lesser elevation of the chloride, sodium and calcium, and a higher magnesium content. Thus, despite carefully controlled experimental procedures in all animals this marked divergence from normal of the electrolyte pattern occurred in the hearts of M12 and M13.

The nitrogen values of all the hearts indicate a relatively similar cell protein (total nitrogen) content, as well as a similar connective tissue mass (collagen nitrogen).

The quantity of neutral fat (1-3%) found in these experimental hearts is normal. The volume of circulatory blood remaining in the hearts of M10, M11 and M12 was approximately the same as found in the control hearts (approximately 25 ml.), while the quantity left in the ventricles of Dog M13 was extremely high (78 ml.) although some of this blood probably represents hemorrhagic extravasation.

TABLE III

PHASE MASS DATA FOR MYOCARDIUM

M = extracellular compartment + intracellular compartment = (F) + (C)
(F) = grams of extracellular compartment = (F)s + (F)u
(F)s = grams of connective tissue solids in the extracellular compartment
(F)u = grams of ultrafiltrate in the extracellular compartment
(C) = grams of intracellular compartment = $(H_2O)c$ + (C)s = 1000 − (F)
(C)s = grams of solids of the intracellular compartment = total solids − (F)s
$(H_2O)c$ = grams of intracellular water per kilogram of muscle
$[H_2O]c$ = grams of water per kilogram of muscle cells

	M Gm	(F) (F)s Gm	(F) (F)u Gm	(C) $(H_2O)c$ Gm	(C) (C)s Gm	$[H_2O]c$ Gm
M 10	1000	34	261	539	166	765
M 11	1000	33	274	526	167	759
M 12	1000	31	452	363	154	702
M 13						
Left Ventricle	1000	33	512	302	153	664
Right Ventricle	1000	32	360	453	155	745

All values are expressed per kilogram of fat-free, blood-free tissue

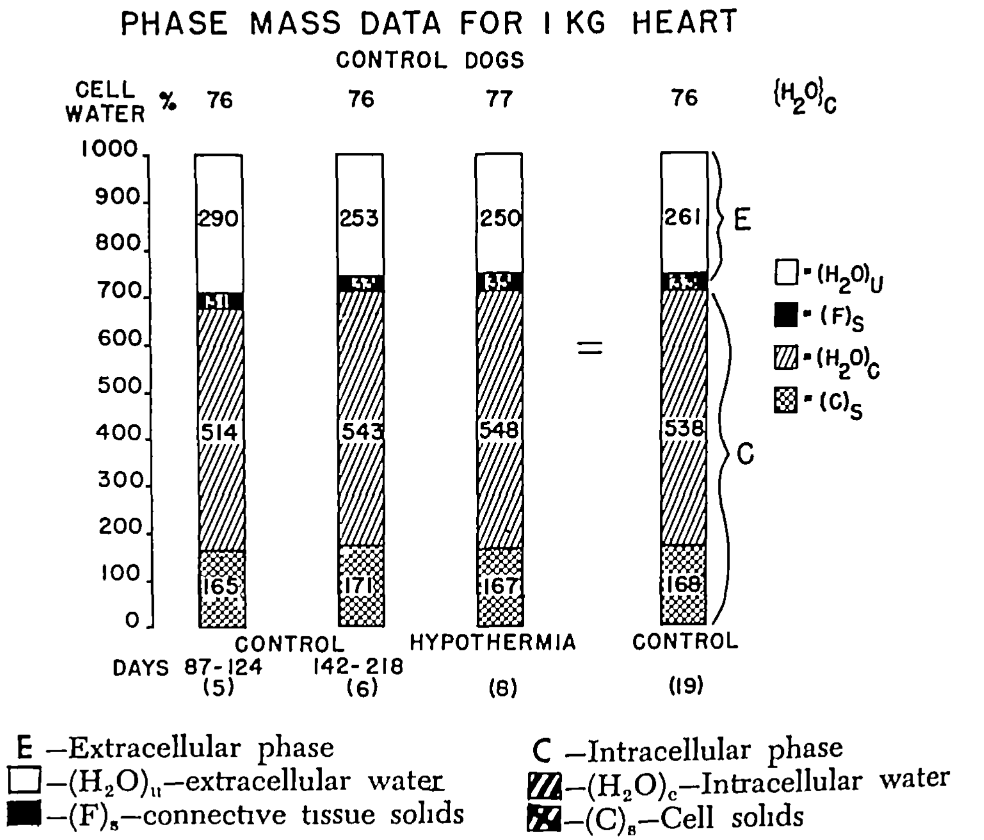


FIG 156 Control data for phases of dog hearts The first two columns represent age control normals[4] indicating a small decrease in extracellular water in the two age groups The third column represents a somewhat older group of dogs that underwent total body hypothermia and these phases as well as cation distribution data fell into the normal range with little deviation and are added with the others to form a group of dogs of an age comparable to those in this study, therefore, column 4 represents the findings on these nineteen dogs

CALCULATED DATA

Table III shows the mass phase data and cell water content on the 4 hearts of the dogs in this study These patterns of the mass of the extra- and intracellular compartments in one kilogram of tissue will be compared with the patterns obtained on a collected control group of normal hearts [1] Since these control groups cover primarily the puppy life span, eight older young adult dogs that were used in experiments following the induction of total body hypothermia[5] were included Therefore, for this presentation the means from the three sets of animals will be used as control values Figure 156 graphically illustrates the mass phase data of

these control animals in groups and as a collective total with a surprising uniformity throughout Graphic comparison of the phase mass patterns of the experimental heart with the collected control groups of hearts shows that M10 and M11 hearts are within normal limits The heart of Dog M12 which was grossly normal functioning adequately and associated with a normal electrocardiogram reveals a large extracellular compartment caused by an increase in the water (extracellular edema) Although the cells show a decreased cell water content it was not enough to account for all of the increase in the extracellular compartment The right ventricle of Dog M13 also reveals an extracellular edema, and the left ventricle which was in rigor has an enormous extracellular compartment mass (with normal connective tissue mass) In the left ventricle the cell water content was low while the contracting right ventricle had a normal cell water content

The partition of the cations potassium and magnesium between the extra and intracellular compartments is given in detail in Tables IV and V The amounts of these cations in the extra cellular compartment are small while the intracellular quantities are large The heart fiber concentrations expressed per kilogram of heart fibers and per kilogram of heart fiber water are graphi

TABLE IV

DISTRIBUTION OF POTASSIUM BETWEEN SERUM AND MYOCARDIUM

[K]f = m.eq of potassium per kilogram of extracellular water
(K)m = m eq of potassium per kilogram of muscle
In (F)uΔCl = m eq in the ultrafiltrate of the extracellular compartment that is not associated with the connective tissue solids
Assoc. c(F)s = m.eq of potassium associated with the connective tissue solids in extra cellular compartment = 3 4 × (F)s/100
In (C) = m.eq of potassium in the intracellular compartment (K)m − K in (F)
[K]c = m.eq of potassium per kilogram of muscle fibers = (K)c/(C) × 1000
[K]c = m.eq of potassium per kilogram of muscle fiber water = (K)c/(H_2O)c × 1000

	[K]f m eq	(K)m m eq	in (F): in (F)uΔCl m eq	in (F): c (F)s m.eq	in (C) m.eq	[K] m.eq	[K]c m eq
M 10	3 00	81 05	0 81	1 16	79 09	112 2	146 7
M 11	3 03	77 08	0 88	1 10	76 00	108 4	142 7
M 12	3 02	51 44	1 45	1 10	48 80	95 5	137 0
M 13							
Left Ventricle	5 12	38 90	2 36	1 12	35 4	77 8	117 2
Right Ventricle	5 12	62 70	1 50	1 09	59 42	98 6	132 4

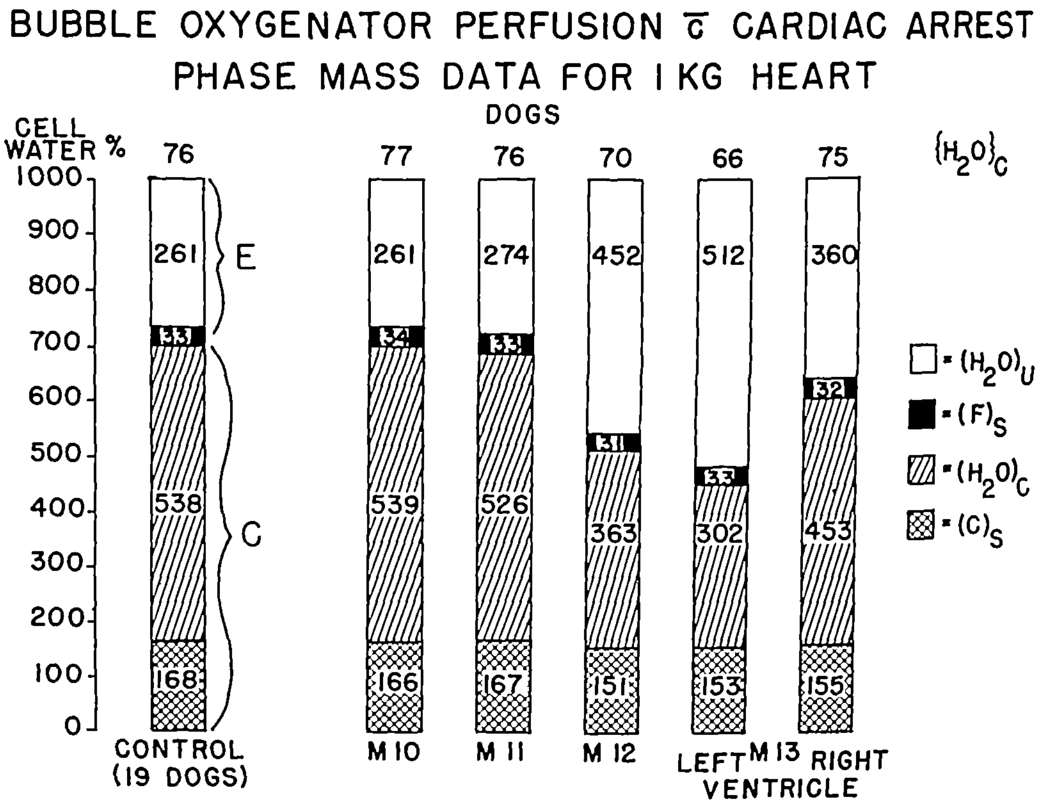


FIG 157 The phase data on the nineteen control dogs (column 1) are compared with the individual experimental findings The findings in M10 and M11 are normal M12 and both ventricles of M13 show an increase in extracellular water and a decreased intracellular water content

cally illustrated in Figures 158 and 159 along with the control values The findings in M10 and M11 again are within normal limits M12 heart has a low cell potassium concentration, but the decreased cell water content brought the potassium concentration to a normal value per kilogram of cell water to normal values Magnesium concentrations in the above three dogs were within normal

TABLE V

DISTRIBUTION OF MAGNESIUM BETWEEN SERUM AND MYOCARDIUM

	[*Mg*]*f* *m eq*	(*Mg*)*m* *m eq*	*Mg in* (*I*) *m eq*	*Mg in* (*C*) *m eq*	[*Mg*]*c* *m eq*	[*Mg*]*c* *m eq*
M 10	1 69	15 04	0 44	14 6	20 7	27 1
M 11	1 54	13 82	0 42	13 4	19 4	25 5
M 12	1 85	11 31	0 85	10 46	20 1	28 8
M 13						
Left Ventricle	1 85	13 48	0 95	12 53	27 5	41 4
Right Ventricle	1 85	18 27	0 66	17 61	28 7	38 9

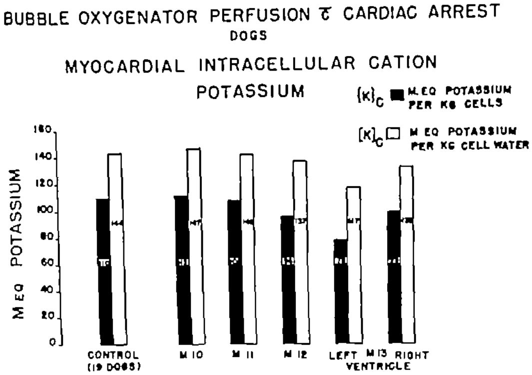


FIG 158 Concentrations of potassium in the cells and cell water of the heart muscle of the nineteen control dogs are compared with the individual experimental data. The findings in M10 and M11 are normal The fiber content of potassium in M12 and M13 is low however with decreased cell waters there is less abnormality in the concentration in this compartment.

values M13 heart on the other hand presents abnormal findings and as anticipated the disturbances are more severe in the left ventricle It will be noted that a marked decrease in the potassium

TABLE VI

DISTRIBUTION OF SODIUM BETWEEN SERUM AND MYOCARDIUM

	[Na]f m.eq	(Na)m m.eq	Na (F) c(F)=Δ(T+c(F)) m.eq	m.eq	ΔNa* m.eq
M 10	152 1	42 20	31 7	6 67	3 72
M 11	152 4	48 83	33 8	6 67	8 35
M 12	152 8	86 1	63 1	6 2	16 8
M 13					
Left Ventricle	152 2	90 9	70 1	6 67	14 1
Right Ventricle	152 2	61 3	4 2	6 40	7 6

Units are expressed per kilogram of blood-free fat-free tissue
*ΔNa = difference between determined sodium and estimated sodium in (F)

of the heart fibers and heart fiber water was accompanied by an increase in the magnesium concentrations

Sodium is primarily an extracellular cation, in fact, for many tissues the sodium values can be used for estimating the extracellular compartment Table VI shows the distribution of sodium in the various sites with a ΔNa indicating the difference between

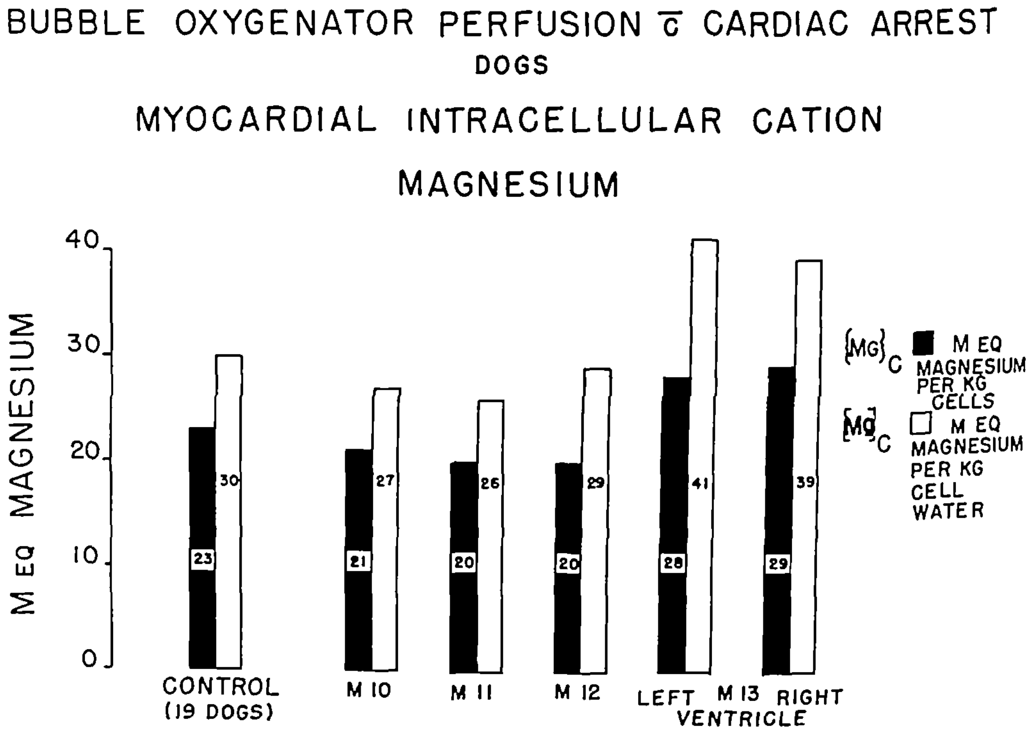


FIG 159 Concentrations of magnesium in the cells and cell water of the heart muscle of the nineteen control dogs are compared with the individual experimental data The findings in M10, M11 and M12 are normal The fiber and fiber water content of magnesium in the ventricles of M13 are high

the calculated concentration of the sodium in the extracellular compartment and the determined sodium of the whole heart muscle The ΔNa in M10 is normal (3 7m eq) Those of M11 and the right ventricle of M13 are somewhat elevated (8 3 and 7 6 m eq), while those of M12 and left ventricle of M13 are quite high (16 8 and 14 1 m eq)

Calculations of the distribution of the calcium are not as precise as those of the other cations since there are no available values for the amount associated with the connective tissue However, after deducting the amount of calcium in the extracellular fluid

TABLE VII

DISTRIBUTION OF CALCIUM BETWEEN SERUM AND MYOCARDIUM

	[Ca]f m eq	(Ca)m m eq	In (F) m eq	ΔCa m eq
M 10	2 01	2 32	0 68	1 64
M 11	2 60	2 70	0 73	1 97
M 12	2 80	6 25	1 27	4 98
M 13				
Left Ventricle	2 37	6 72	1 22	5 50
Right Ventricle	2 37	3 42	0 85	2 57

ΔCa = difference between determined calcium (Ca)m and estimated calcium in (F)

from the total determined calcium values there remains an amount of calcium labeled ΔCa Normally this ΔCa is about one milli equivalent The ΔCa for the hearts of M10 and M11 are normal (1 6 and 1 9 m eq) that of the right ventricle of the myocardium of M13 is elevated (2 6 m eq) and those of M12 and the left ventricle of M13 are extremely high (4 98 and 5 5 m eq)[1] See Table VII

DISCUSSION

These studies on a few animals have been fortunate in that two corroborated chemically the apparent normality of the heart following the experimental cardiac by pass with the use of a pump-oxygenator (bubble type) and elective cardiac arrest while one heart, to all appearance normal proved to have an extra cellular edema and moderate disturbances in cation distribu tion The fourth heart was in obvious mortal difficulty with these biochemical abnormalities even more severe

The only common abnormality found in all of the experimental dogs was a final metabolic acidosis indicated by a low serum pH lowered buffer base and an elevated fixed acid (serum chloride content) (Fig 155)[2]

The acute extracellular edema found in the myocardium of Dogs M12 and M13 is not explainable at present Evidently the heart fibers compensated in part for the large increases in the extracellular fluids with the result that the cell water decreased somewhat (Fig 157) but not enough for complete compensation the remainder must have been acquired from the vascular bed The shift of water from the cellular compartment of a tissue to

of the heart fibers and heart fiber water was accompanied by an increase in the magnesium concentrations

Sodium is primarily an extracellular cation, in fact, for many tissues the sodium values can be used for estimating the extracellular compartment Table VI shows the distribution of sodium in the various sites with a ΔNa indicating the difference between

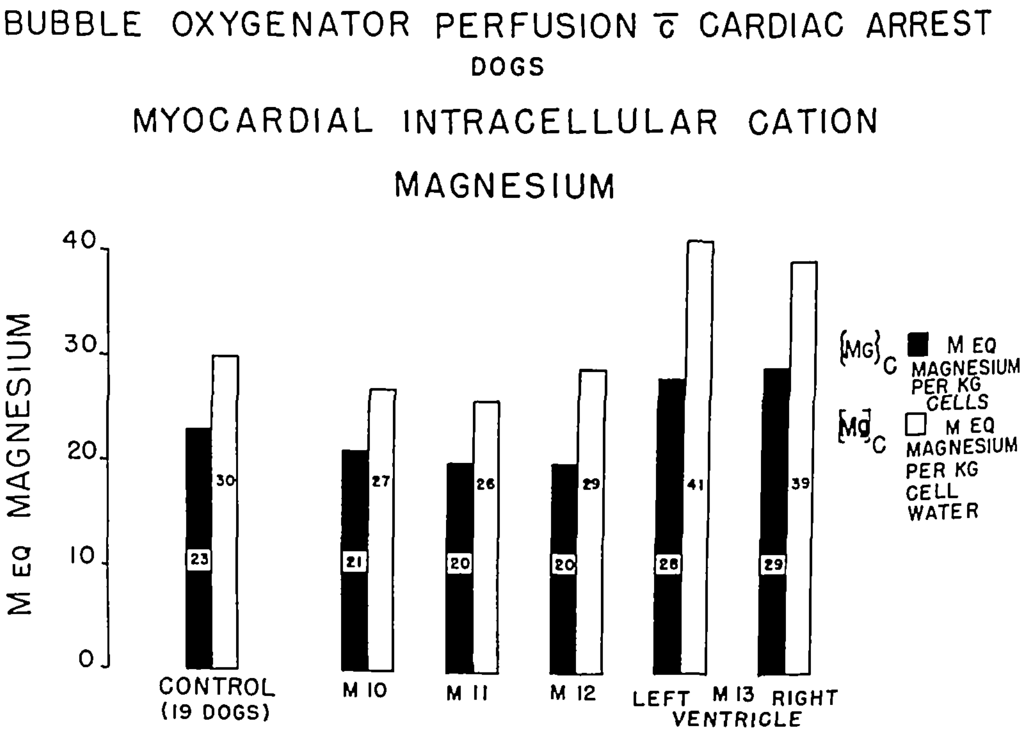


FIG 159 Concentrations of magnesium in the cells and cell water of the heart muscle of the nineteen control dogs are compared with the individual experimental data The findings in M10, M11 and M12 are normal The fiber and fiber water content of magnesium in the ventricles of M13 are high

the calculated concentration of the sodium in the extracellular compartment and the determined sodium of the whole heart muscle The ΔNa in M10 is normal (3 7m eq) Those of M11 and the right ventricle of M13 are somewhat elevated (8 3 and 7 6 m eq), while those of M12 and left ventricle of M13 are quite high (16 8 and 14 1 m eq)

Calculations of the distribution of the calcium are not as precise as those of the other cations since there are no available values for the amount associated with the connective tissue However, after deducting the amount of calcium in the extracellular fluid

cardial calcium content, so that some other factor such as ioniza tion must be considered if the excess calcium is to be implicated

It must be emphasized that these abnormalities occurred fol lowing two separate procedures perfusion and arrest and at present cannot be separated Furthermore these data should be interpreted only to indicate what can happen under these cir cumstances (two animal hearts were normal) and are not neces sarily a common occurrence In retrospect we have noted that these four experiments were performed at a time of personnel change and this could contribute to the factor of adequacy of the mechanics of the perfusion

If the edema seen in the normal appearing heart of M12 is a generalized finding then this may be a clue to some of the prob- lems in this field such as obvious cerebral complications delayed "unexplained" deaths and difficulties in measuring blood balance Cerebral edema could explain the first two findings which at present, are being related to fibrin and air emboli Any generalized edema would falsify weight studies as an indicator for determin ing the adequacy of blood transfusions

On the basis of these findings a few animals showing some cere- bral disturbance after thirty minutes of perfusion have been given 50 per cent glucose intravenously and have showed a temporary response however other forms of cerebral damage might be associated with edema and respond similarly

SUMMARY

Water electrolyte and nitrogen content of the blood and myo- cardium were observed in normal dogs before (control series for myocardium) and after the experimental production of a cardiac by pass with the use of the bubble type of pump-oxygenator and elective cardiac arrest with potassium citrate The pertinent find ings may be summarized as follows

1 The common abnormality found in the four experimental dogs was a final metabolic acidosis indicated by a low serum pH lowered buffer base and an elevated serum chloride content

2 The histochemical characterization of the experimental hearts from the four dogs showed that two of them corroborated chemically the apparent normality of the heart while the other

the interstitial fluid compartment is always caused by a decrease in the osmotic pressure within the cells. Since the osmotic pressure of intracellular fluids is largely determined by the concentration of potassium and since potassium was found to be low, some shift in water resulted.

A loss of the main cellular cation, potassium, is generally associated with a gain of some other cation in order to maintain osmotic equilibrium within a tissue. Many investigators[13, 14] have shown that when potassium leaves a tissue cell, sodium enters. If we assume that the ΔNa values represent the amount of sodium that entered these heart fibers after the loss of the potassium, the amount of sodium that entered the cell can be calculated. For example, in Dog M12 the ΔNa was 16.8 m.eq. per 363 gm. of intracellular water or 46.2 m.eq./kg. of heart fiber water, or in the left ventricle of M13 the ΔNa was 14.1 m.eq. in 302 gm. of intracellular water or 46.6 m.eq./kg. of heart fiber water. It seems, therefore, that under the conditions of these tissues some sodium has entered the muscle fiber. Interestingly enough these two dogs also showed large losses of intracellular potassium, the figures for $[K]_c$ being 137.0 and 117.2 m.eq. Since the water of the heart fibers decreased to such an extent that the percentage of heart fiber water was lower than in the control heart and the potassium concentration was also low, there is evidence that the internal structure of the heart fibers must have changed during this experimental period.

The calculations on these data assume metabolizing tissue, and the actively contracting state of all except the left ventricle of M13 strengthens this assumption.

The large quantities of calcium found in the hearts of M12 and the left ventricle of M13 cannot be explained at this time. Work is in progress seeking an explanation. The presence of rigor in the left ventricle of M13 is similar to that produced experimentally with an excess of calcium, which is relieved by infusion of potassium salts. This rigor has been seen on occasion in the deteriorated heart, experimentally and clinically, and has failed to respond to potassium infusion (even into the coronary system). It should also be noted that the heart of M12 was contracting normally while the other was in rigor and both had similar myo-

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two had an acute extracellular edema accompanied by dehydration of the heart fibers In the two abnormal hearts there was a striking reduction of the heart fiber potassium content and the probability that some of the loss of intracellular potassium was compensated by a gain in sodium

3 A marked divergence of the electrolyte patterns from normal was associated with the changes in the volume relationships between the extra- and intracellular phases in these hearts

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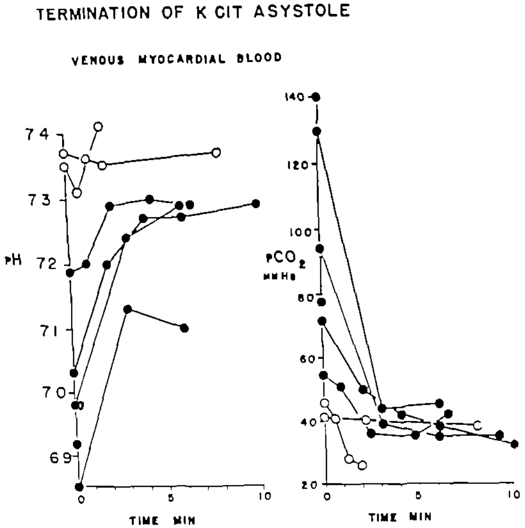


Figure 161 (Pontius)

In this latter group there were numerous determinations indicating a marked acidosis of the venous blood with pH values as low as 6 85 This acidosis was not only metabolic but also respiratory as indicated by large values of pCO_2 in the venous blood leaving the myocardium

Measurements of oxygen and carbon dioxide exchanges during the recovery period were made and shown in Figure 160 It is noted that there was frequently a two to three fold increase in carbon dioxide release during the first few minutes of this period, and that oxygen consumptions had a much smaller variation

DR ALBERT B LOWENFELS New York I would like to comment on Dr Glenn s paper dealing with coronary flow during total body perfusion

DISCUSSIONS ON METABOLISM OF THE HEART

DR ROBERT G PONTIUS, Boston We have been interested in the metabolism of the arrested heart as it resumes its normal cardiac action, and have measured coronary blood flow, blood pH values, oxygen and carbon dioxide gas exchanges

In a series of experimental animals extracorporeal circulation was established and potassium citrate arrest induced, Figure 161 Upon termination of the arrest, usually after thirty minutes, a series of determinations were made on coronary blood, using simultaneous arterial and venous blood samples, in an attempt to establish the metabolic pattern as the heart progressed from arrest toward resumption of normal action The observations in instances of resumption of normal sinus rhythm within two minutes are indicated by circles and those instances of delays of more than three minutes are indicated by dots, Figure 161

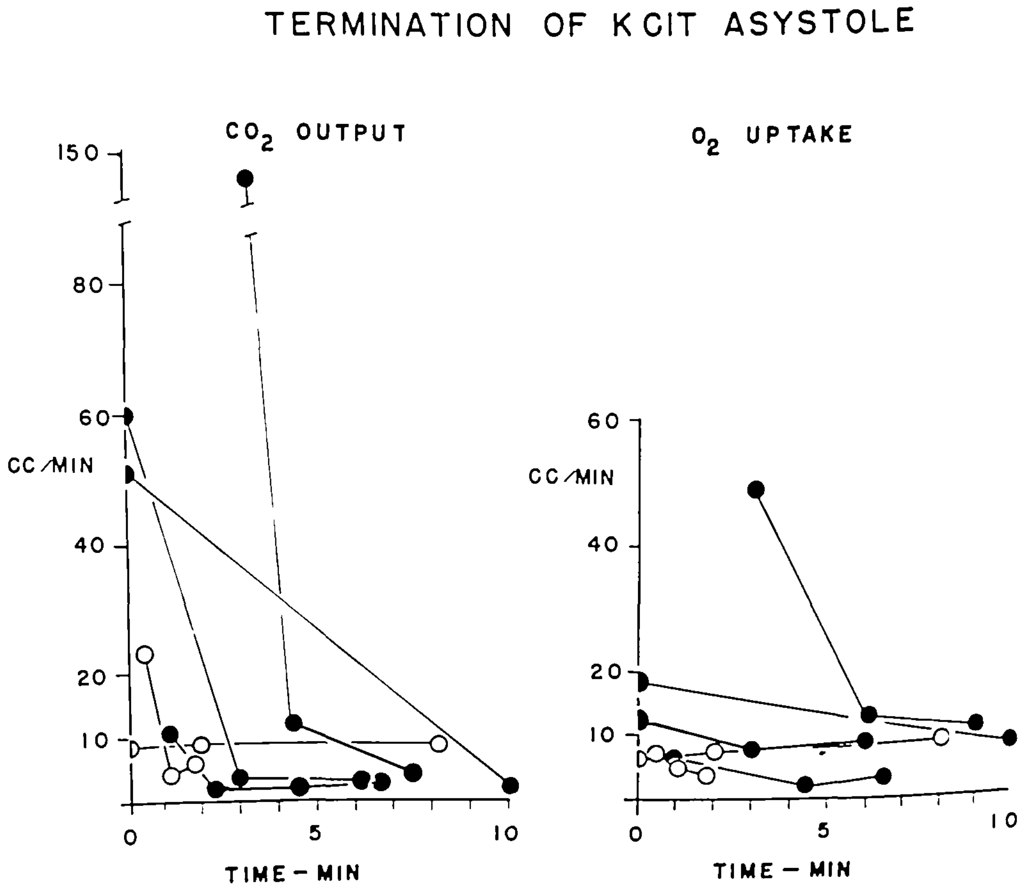


FIGURE 160 (Pontius)

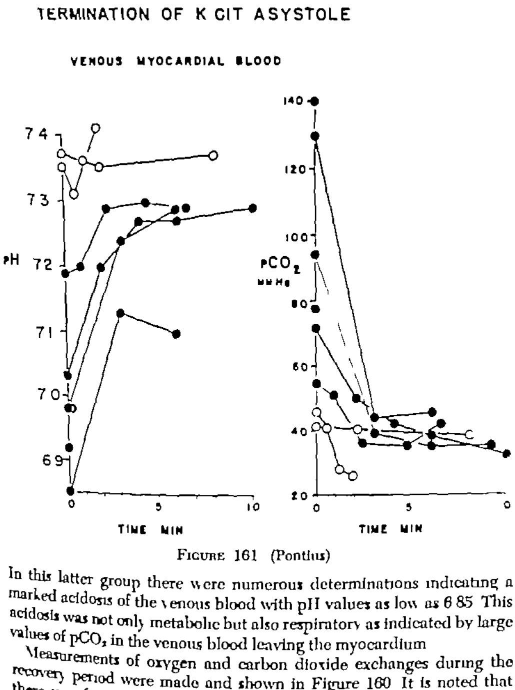


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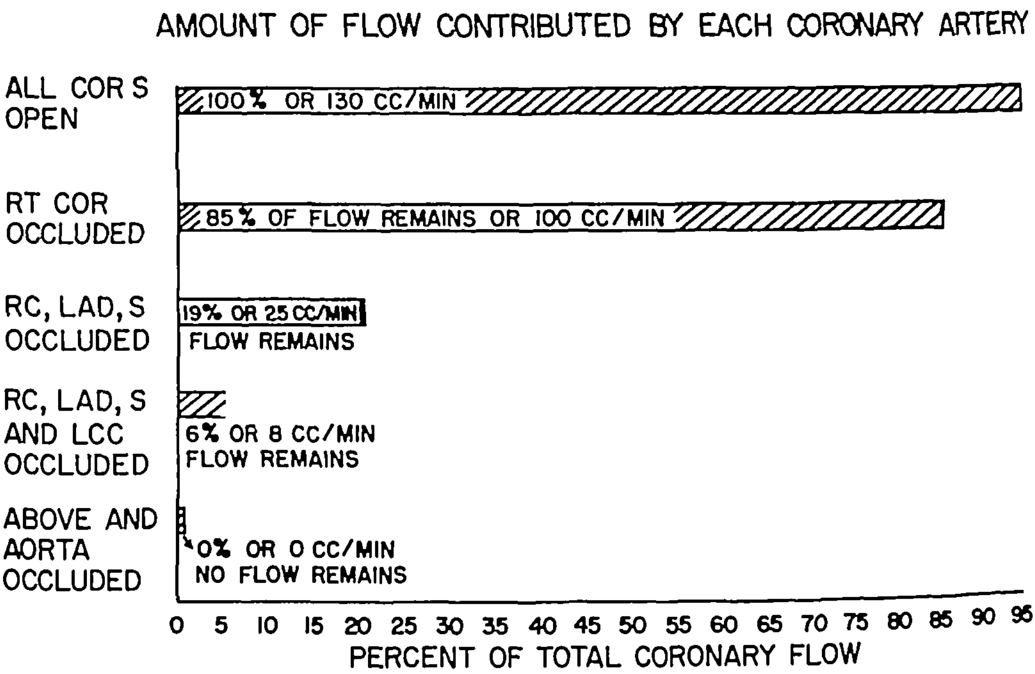


FIGURE 162

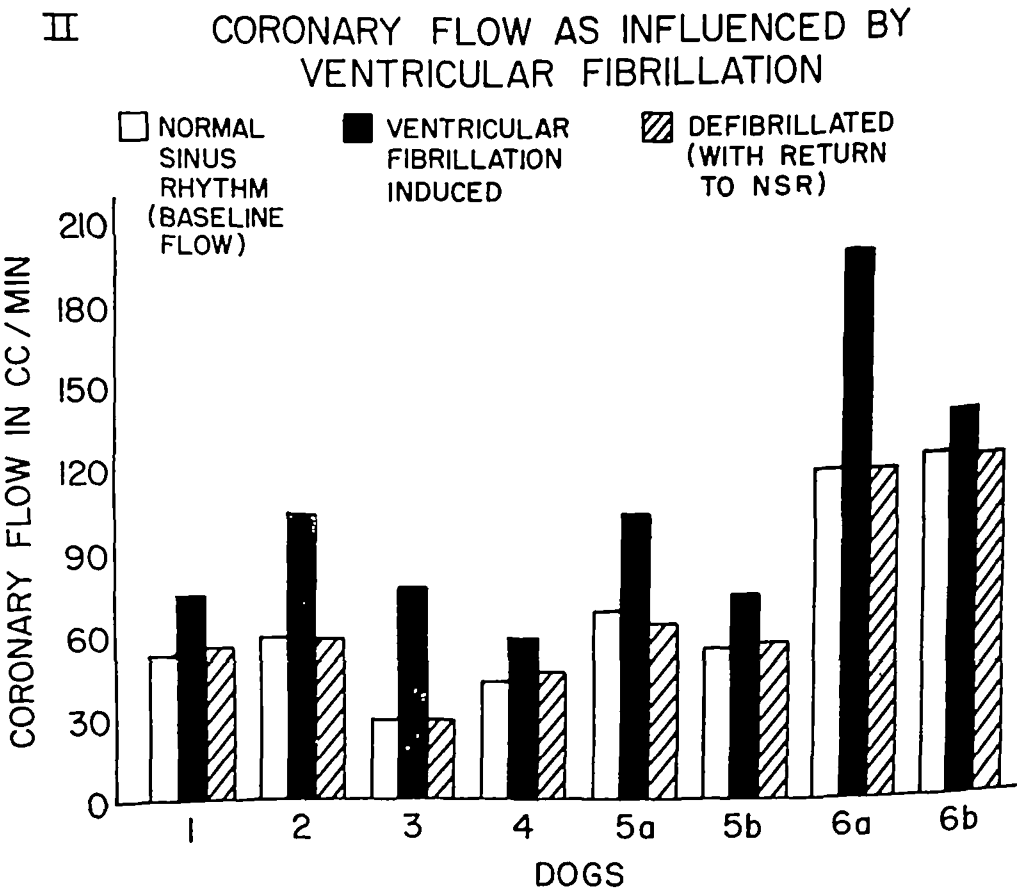


FIGURE 163

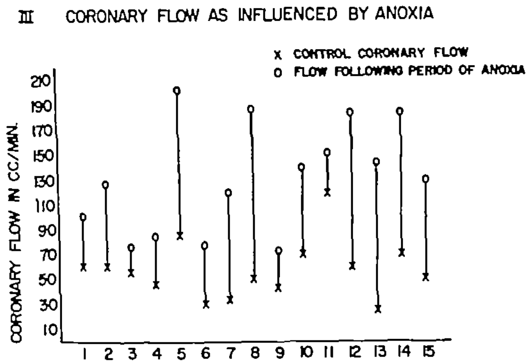


FIGURE 164

Our experimental set up was that of total body perfusion using a large bubble oxygenator A catheter was placed in the right main pul monary artery and the coronary venous blood collected We used a graduated cylinder and a stop watch to measure the venous return

In Figure 162 are shown data from a group of dogs The crosshatches are control values for coronary blood flow Following this the aorta was cross-clamped and blood flows were measured after a three minute period of occlusion Like Dr Glenn we can point to a tremendous in crease in the coronary blood flow following release of coronary occlu sion

Data from a group of six dogs showing the effect of ventricular fibril lation on coronary blood flow are presented in Figure 163 The black boxes represent control coronary flow Subsequently ventricular fibril lation was produced electrically and in every instance the blood flow increased When the ventricular fibrillation was abolished, the coronary blood flow returned almost to normal values

We were interested in the partition of blood flow between the various coronary arteries Figure 164 The top horizontal column represents 100% blood flow through the coronary arteries in a single canine ex periment. Then we performed serial ligations of all the coronary

arteries and the remaining columns show the effect of these ligations on the total coronary flow

DR JOHN F PERKINS, JR, Chicago I would like to call to your attention two terms used by Sir Thomas Lewis about thirty years ago The first term is "reactive hyperemia," which has been mentioned so often with regard to the increased blood flow seen after release of occlusion of the artery to an arm This is in contrast to "active hyperemia," which occurs during exercise In the heart this reactive hyperemia is presumably going on all the time In these two types of hyperemia, there is active dilatation of the arterioles and also capillaries, due to the release of various metabolites such as lactic acid Dr Pontius said something very interesting in this connection, in that he found both metabolic and respiratory acidosis in blood taken immediately after occlusion of an artery This metabolic acidosis was, of course, due to the addition of lactic acid which depletes the blood bicarbonate, and the respiratory acidosis in his experiment was due to the accumulation of CO_2 which was not yet washed out by the lungs The respiratory acidosis will soon be corrected by the action of the respiratory center, producing increased ventilation and removal of the excess CO_2

DR JOSEPH W GILBERT, Bethesda We have employed a modified Langendorff preparation in the study of myocardial metabolism during elective asystole, perfusing the arrested heart with arterial blood containing potassium citrate Oxygen consumption, CO_2 production, and the extraction of carbohydrate and fatty acid substrates have been found to be markedly reduced during diastolic arrest when the chambers of the heart are empty If, however, the heart is allowed to distend during cardio-pulmonary by-pass with blood from the coronary sinus and pulmonary veins, its metabolic requirements are considerably increased This underscores the need for decompressing the arrested by-passed heart in order to prevent dilatation and to facilitate restoration of satisfactory contraction

Yesterday Doctor Moore suggested the use of curare to reduce the oxygen requirement of the musculature during total body perfusion Because of the role of potassium in familial periodic paralysis, wherein metabolism is substantially diminished, we have perfused the hind limb of the dog with arterial blood containing potassium citrate in approximately 3% concentration and have observed a marked decrease in oxygen extraction across the skeletal muscle under these conditions I

don t of course feel justified in drawing conclusions from this single observation made—in fact—just before leaving for this meeting but in the light of Doctor Moore s suggestion the finding seemed provocative

DR. CHARLES DUBOST Paris I would like to start with a preliminary report concerning a story about coronary circulation in total body perfusion

We have used the method shown in Figure 165 to measure coronary blood flow This technic involves the placement of a catheter in the coronary sinus and another in the pulmonary artery

This slide shows the results of our measurements with the aging of the preparation. Each succeeding measurement is separated from the next by ten to fifteen minutes Figure 166

This slide shows the influence of the artificial output on the heart rate Figure 167

This slide shows an excellent relationship between the coronary flow and the artificial output You see that it is represented by a straight line Figure 168

This slide shows the relationship between systemic flow and systemic pressure, Figure 169

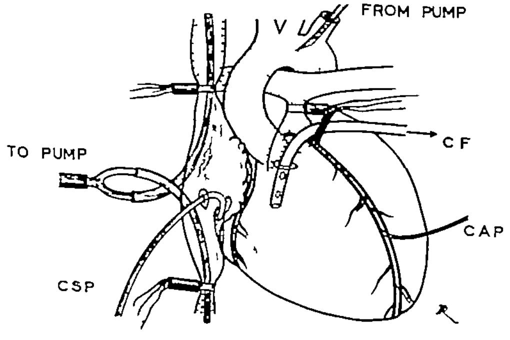
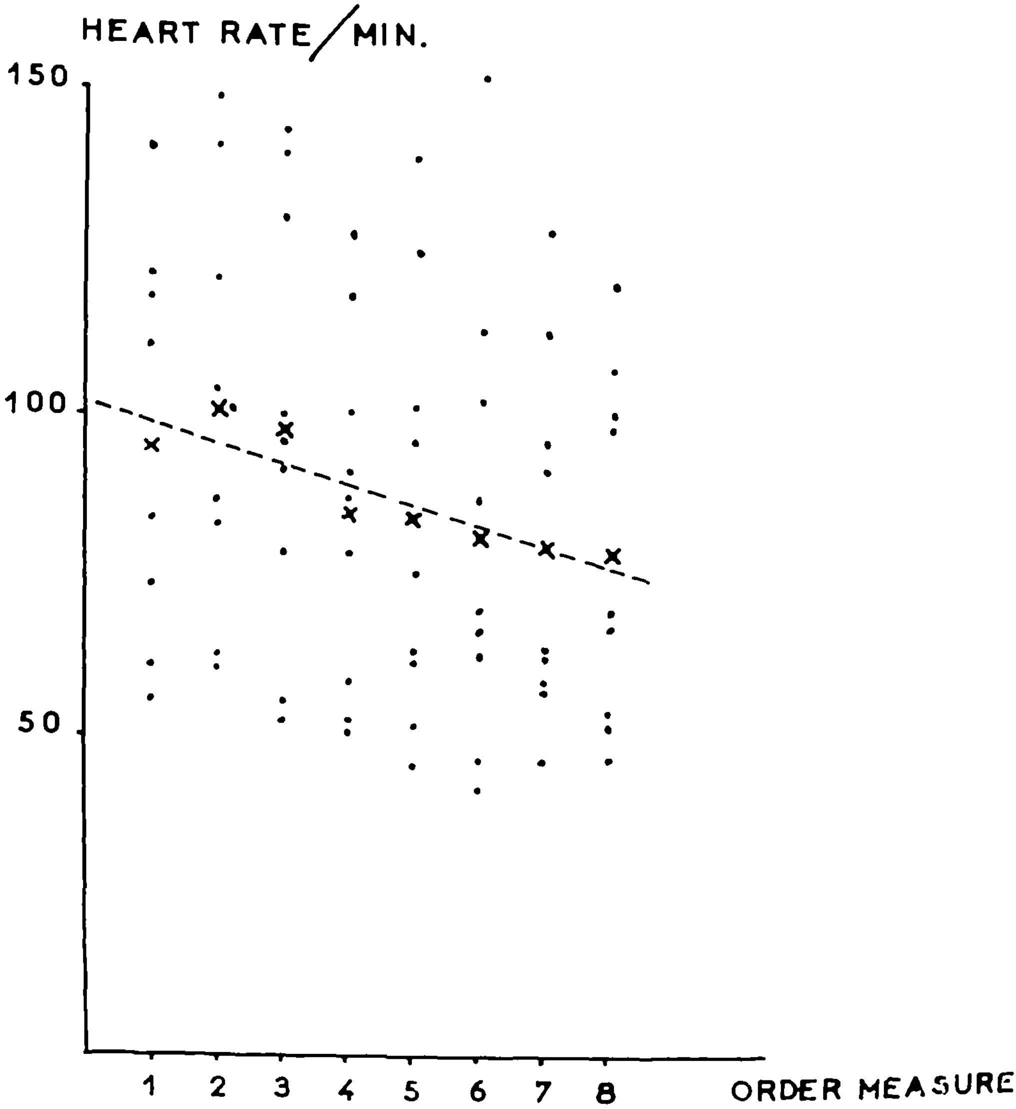


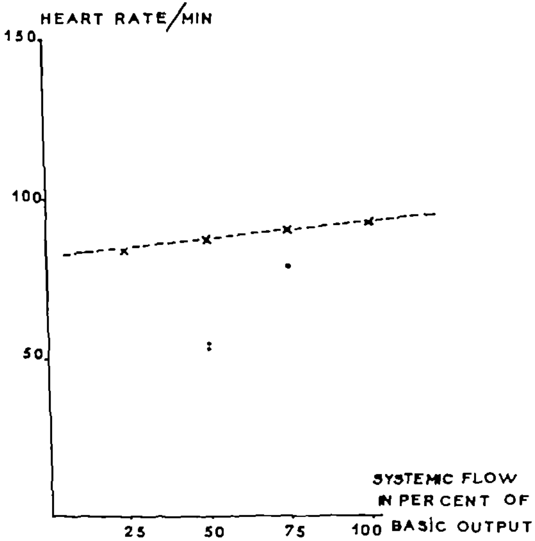
FIGURE 165 (Dubost)



Number measure	1	2	3	4	5	6	7	8
Mean HR	95	101	98	85	84	81	80	79
Standard deviation	29	31	33	27	33	32	28	27

Figure 2 showing diminution of heart rate with "aging" of the preparation (Each successive measure is separated from the next by 10 or 15 minutes, it is represented by its number or order)

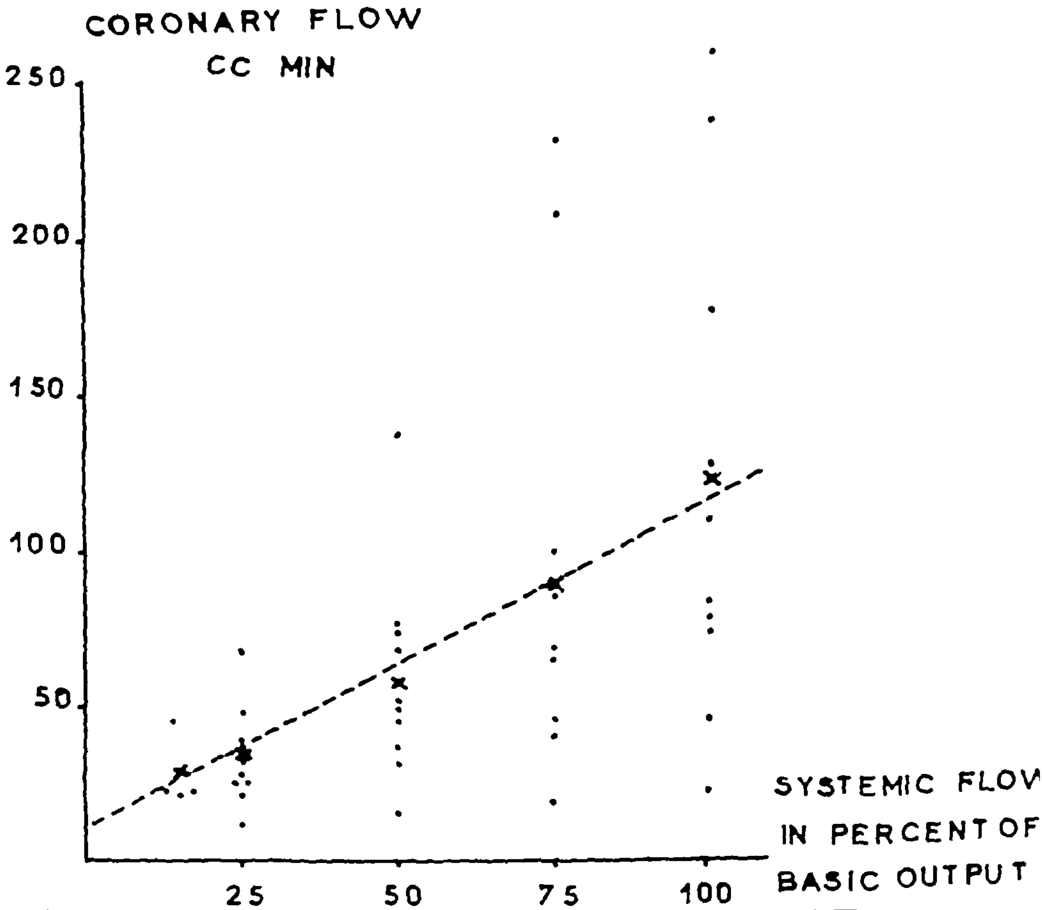
FIGURE 166 (Dubost)



Systemic flow, in per cent of basic cardiac output	25	50	75	100
Mean HR	84	87	90	92
Standard d viation	26	30	28	37

Figure 3 showing the influence of artificial output on heart r te

FIGURE 167 (Dubost)



Systemic flow in per cent of basic cardiac output	AF	25	50	75	100
Mean Cor. Fl.	28	33	60	90	123
Standard deviation	13	16	34	71	82

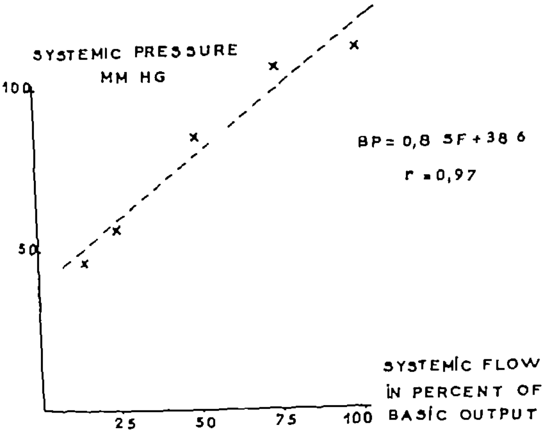
Figure 4 showing the excellent correlation between coronary flow and artificial output (AF = minimum flow permitting survival)

FIGURE 168 (Dubost)

This shows the diminution of the A-V difference in oxygen as the artificial systemic output increases, Figure 170

This shows the stability of oxygen consumption at 75 and 50 per cent of the basic cardiac output, and the decrease at 25 per cent, Figure 171

In summary we can say that the heart rate is markedly slowed during our experiments Cooling of the myocardium plays an important part, but sometimes it is not the whole effect, and other factors are sub-

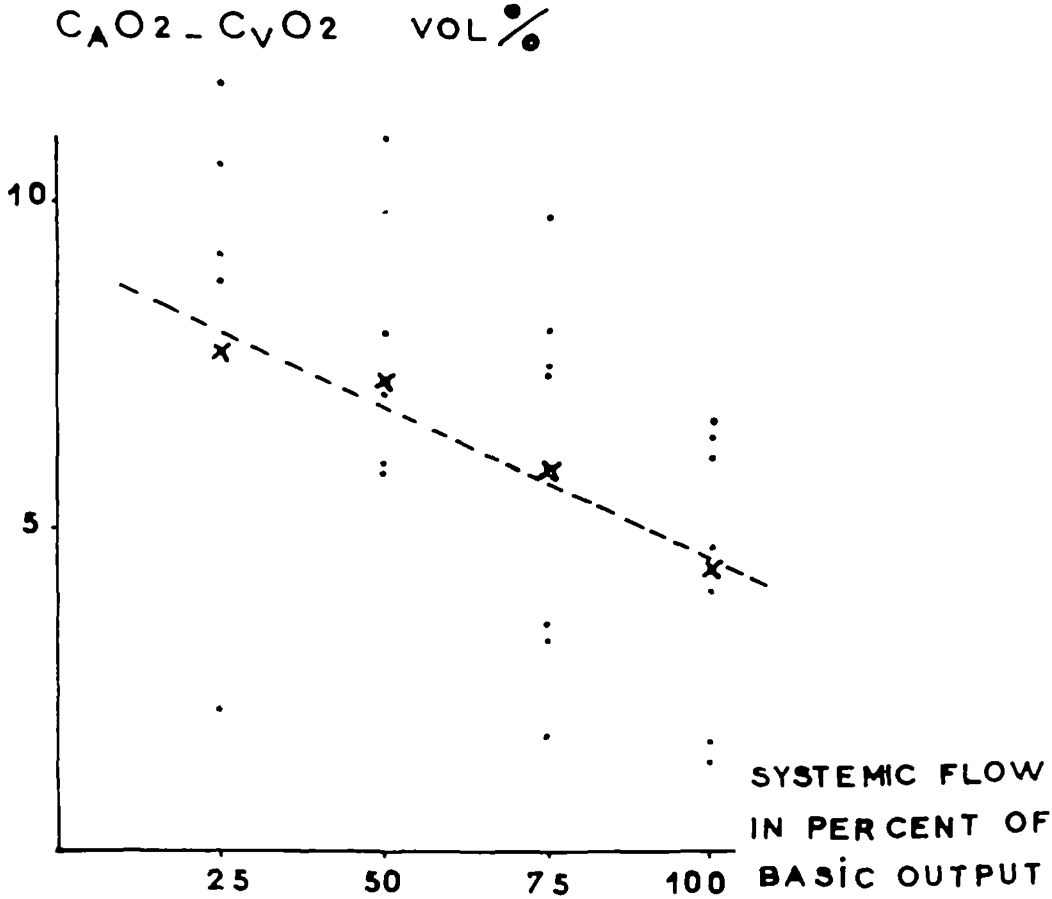


Systemic flow in per cent of basic cardiac output	AF	25	50	75	100
Mean Syst Pres	46	57	85	106	111
Stantard deviation	15	14	17	16	19

Figure 7 showing the relation between systemic flow and systemic pressure. (AF = minimum flow compatible with survival)

FIGURE 169 (Dubost)

mitted for explanation. Coronary flow is a simple linear function of artificial systemic flow and of the mean arterial pressure as the latter it literally linked with the former Oxygen consumption in the by passed heart remains constant when artificial flow decreases from 100 to 50 per cent of the basal cardiac output, but oxygen consumption diminishes markedly at the 25 per cent level These findings have led us to think that extracorporeal circulation for surgical purposes should be performed under artificial flows higher than 25% of the basal cardiac output



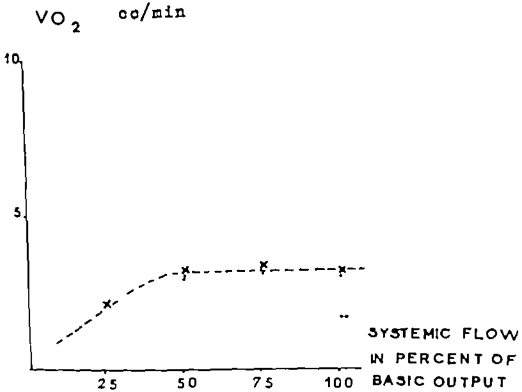
Systemic flow in per cent of basic cardiac output	25	50	75	100
Mean CaO_2-CvO_2	7,75	7,30	5,89	4,45
Standard deviation	3,33	2,64	2,83	2,18

Figure 5 showing the diminution of arterio venal difference in oxygene when artificial systemic output is increasing.

FIGURE 170 (Dubost)

DR STANLEY J SARNOFF, Bethesda I think it is rather disturbing to consider the data which indicate that the oxygen consumption of the arrested heart, as Dr Bing told me last night, is somewhere between 30 and 40 per cent of the beating heart This is a biological phenomenon which I find very difficult to reconcile with my own experiences

Dr Winterscheid's figures were very interesting in that with a little



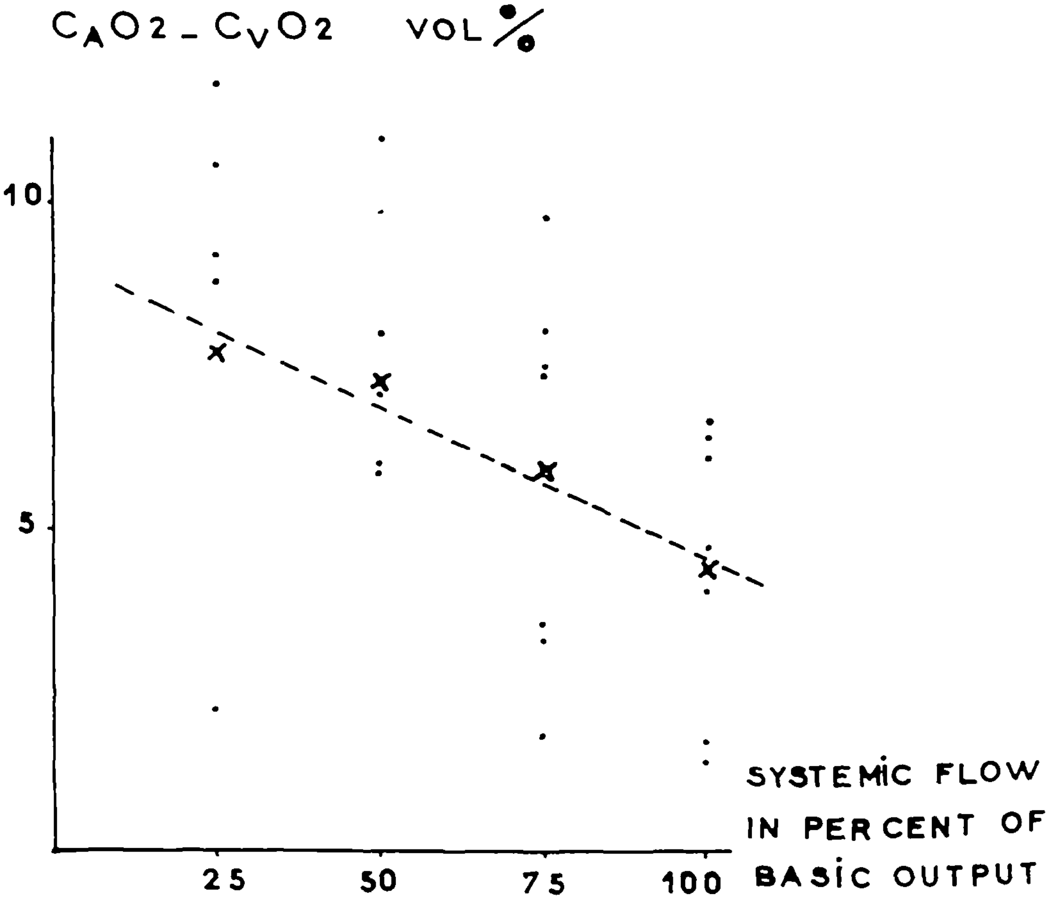
Systemic flow in per cent of basic cardiac output	25	50	75	100
Mean VO_2	1 98	3 10	3 29	3 13
Standard deviation	0 81	1 86	2 01	2 03

Figure 8 showing the stability of oxygen consumption at 100 75 and 50% of basic cardiac output, and its decrease at 25%

FIGURE 171 (Dubost)

rough calculation one comes up with an oxygen rate under experimental conditions at least, which is not very different from oxygen consumption of the skeletal muscle and little different from what the rest of the cardiac muscle is going to be which had a 30 to 40 per cent oxygen utilization during arrest

It is difficult for me to understand how 30 to 40 per cent of the baseline beating oxygen consumption can keep going on with no oxygen being added to the myocardial system and still have the heart retain the appearance of containing oxygenated blood I think this is extraordinarily important and probably best can be solved by the isolated preparations used by Dr Winterscheid



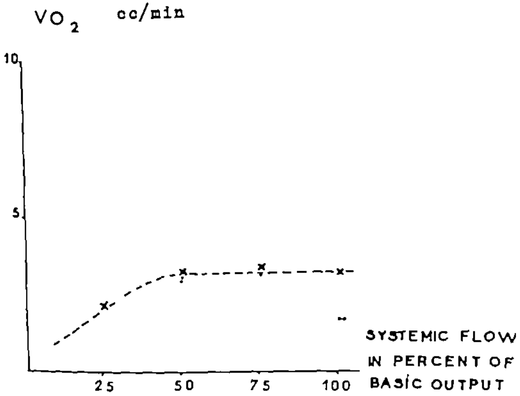
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Systemic flow in per cent of basic cardiac output	25	50	75	100
Mean VO_2	1 98	3 10	3 29	3 13
Standard deviation	0 81	1 86	2 01	2 03

Figure 6 showing the stability of oxygen consumption at 100 75 and 50% of basic cardiac output, and its decrease at 25%

FIGURE 171 (Dubost)

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In the past two years my colleagues and I have been concerned quite a bit as to what tension is required by the normal myocardium Information as to the characteristics *in vitro* remain indistinguishable from the *in vivo* data, for a period of 24 to 48 hours from that of the failing heart It became evident to us that in the beating heart, two things occur There is a development of a tension which shortens stroke volume It became evident that fiber shortening or stroke volume has nothing, or almost nothing, to do with the energy requirement of the myocardium, and that its total energy requirement or almost total, is somewhere between 2 and 5 per cent The almost total energy requirement of the damaged heart is determined by the amount of tension which the myocardium develops I think this probably has some very practical implications

On the basis of this, I think it is necessary to know the aortic pressure in two different conditions It is clear that the coronary flow will go to the coronary vascular bed and may be measured The aortic pressure is graded and this fact is important However, aortic pressure has a very much more important connotation in my mind, and that is it represents the amount of tension which the myocardium develops, and, therefore, sets its oxygen requirement, and the level of the local pO_2 in a measure It acts as a hydraulic force, since it is an expression of the oxygen requirement of the heart which largely determines its needs for energy

PHARMACOLOGY OF THE HEART

By

HENRY SWAN, M D , *and* VERNON MONTGOMERY, M.D , PH D

HAVING no specialized knowledge of pharmacology outside of day to-day therapeutics we have found the assigned task a particularly difficult albeit challenging one In attempting to limit this discussion on the pharmacology of the heart, these thoughts have occurred to us Since the heart is the effector organ of so many homeostatic reflexes almost any agent which has a significant effect on the organism as a whole will have at least a secondary effect on the heart Also since the heart is composed of a mixture of tissues including arteries nerves ganglia and smooth muscle a large number of pharmacological agents which are used for specific effect on one of these tissues will also have a side effect on the heart We have eliminated agents causing only secondary effects from discussion in this presentation

This limits our present consideration to those agents which have a direct effect on the function of the myocardium of the heart. Even here the emphasis will be placed on those agents which seem to be most useful to us as surgeons interested in exerting a positive influence on and occasionally complete control of cardiac function

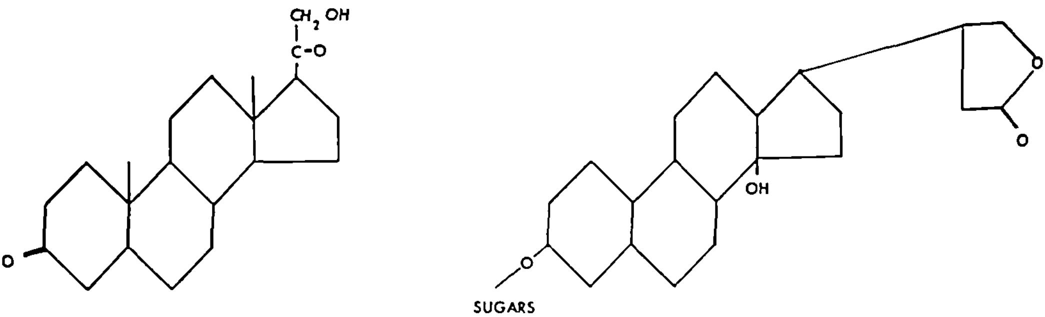
Let us begin with those agents whose primary pharmaco-dynamic property is their ability to increase the tension developed by myocardial tissue that is digitalis and similar glycosides The chemistry of the cardiac glycosides has been the subject of extensive investigation As you recall digitalis compounds are composed of two separate moieties—the aglycone and the one to four sugar molecules attached to it The principal pharmacologic properties of the glycosides lie in the aglycone since the sugars

From the Department of Surgery University of Colorado School of Medicine Denver

are thought to affect only the rate of action through cellular permeability and water solubility

The aglycones have the familiar cyclopentaperhydrophenanthrene nucleus shown in Figure 172, which is also seen in the steroid hormones and bile acids The interesting similarity in structure between digitalis and 11-desoxycorticosterone includes a linkage at the 17 position of a ketone and at the 3 position of an available oxygen

Now what effect do these particular molecules have on the heart? After years of indecision in the literature, it now seems



DESOXYCORTICOSTERONE DIGITALIS

FIG 172 Similarity in the chemical formulas of two agents effecting myocardial contraction is illustrated

firmly established that the primary action of these drugs on the failing heart is that of producing an increase in the strength of contraction This was demonstrated most effectively by Gold and Cattell in 1940,[1] when studying the force of contraction of the cat papillary muscle Their experiment showed clearly that ouabain has a potent, direct effect on the force of contraction of the muscle even though it is completely severed from all body connections and even though no change in rate is permitted

The question of how digitalis produces this effect is a subject of extensive current investigation Many have shown that the failing heart is an inefficient heart There is no decrease in the oxidative metabolism of the heart, but there is a failure to convert this oxidative energy into mechanical work Digitalis-like agents have been shown to correct this overall effect, that is, they re-

store the efficiency of the heart. As yet no specific enzymatic reactions have been shown to be effected by these compounds unless enormous quantities are used and as yet no direct effect of digitalis on actomyosin fibers has been noted. However, many workers have shown that digitalis causes the myocardium to lose potassium. This observation on the intact animal dovetails nicely with recent work by Szent Gyorgyi.[2] While studying the classical phenomenon of treppe he noted that the descending stair effect appeared much more readily when the solution bathing the isolated frog's heart muscle was some artificial media rather than plasma. Analysis for the active ingredient in plasma was made; it proved to be a steroid. Of the many known biological steroids only desoxycorticosterone had a really potent capacity for diminishing the treppe effect. Digitalis and related cardiac glycosides also had this effect. Their chemical similarity has already been referred to.

In Figure 173 we have tried to give you a simplified version of what Szent-Györgyi[2] thinks this means (with apologies to him).

The contractile mechanism within the muscle cell resides in

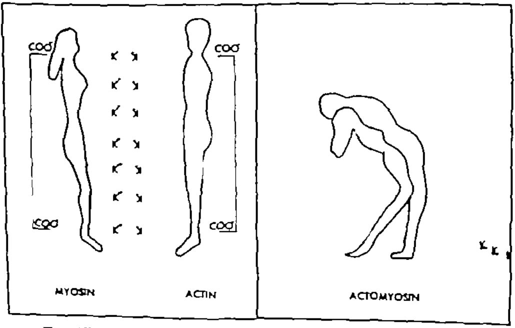


FIG. 173. An interpretive portrayal of the electro-physical forces relating to muscle fiber contraction.

are thought to affect only the rate of action through cellular permeability and water solubility.

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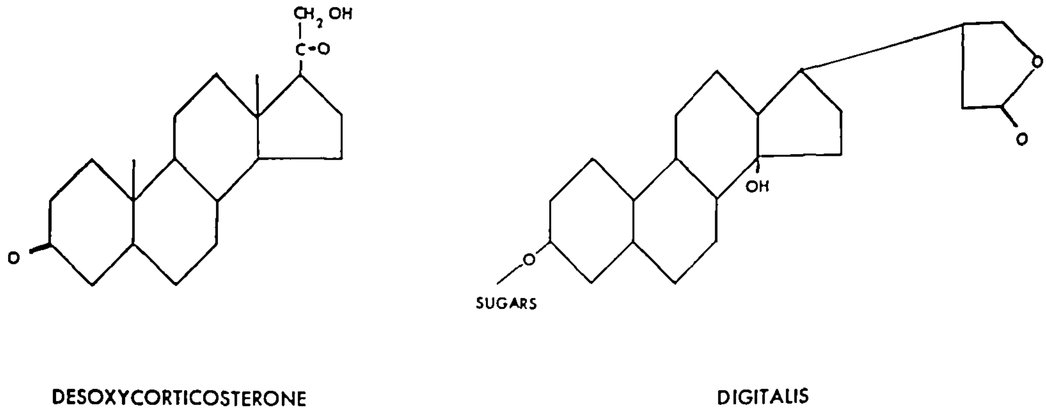


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magnitude of this reversal of membrane potential i e the action potential is proportional to the pre-existing difference between intracellular and extracellular sodium concentrations

In summary then the *resting* potential (with the inside of the cell electrically negative to the outside of the cell) is determined primarily by the difference in concentrations of potassium in these two areas With stimulation of the conducting tissue the selective permeability of the membrane is lost sodium suddenly moves in

RESTING POTENTIAL (VOLTS) OF MYOCARDIAL FIBER

IN TERMS OF POTASSIUM DISTRIBUTION

$$E = 0.059 \log \frac{[K^+]_i}{[K^+]_e}$$

FIGURE 174

the direction of the concentration gradient—to the inside—and the *action* potential results At the same time potassium moves in the direction of its concentration gradient i e out of the cell, and contraction shortly follows by virtue of the actomyosin mechanism previously described The recovery process involves removal of the sodium and return of the lost potassium with the resulting restoration of the resting membrane potential

In the light of the above considerations we can discuss briefly the *mechanism* of action of potassium on the heart. In 1952 we recommended the clinical use of this ion to combat ventricular fibrillation, and more recently it has been widely used to deliberately arrest the beat of the heart, a matter concerning which we will hear much more this afternoon.

First, we need to know what happens to the potassium placed in the extracellular fluid Direct evidence on the heart is not readily available But if we look at Figure 175 from the work of Boyle and Conway we see such data derived from skeletal muscle One will note that as the external potassium is increased

the long, thin fibrous protein, myosin As with all such molecules it has the tendency to shorten by folding on itself At normal intracellular pH, this protein has negative charges in excess of positive, mediated through the dissociation of the carboxyl groups These do two things they repel each other, thus keeping the protein extended in a straight position, and they electrostatically bind potassium ions Necessary for contraction is union between myosin and an adjacent actin molecule For purposes of simplification, the actin molecule, which is really a globular protein, is depicted as a long protein, too It is also surrounded by a cloud of potassium ions The repelling force of the potassium ions keeps the two protein molecules separated When the wave of depolarization passes over the membrane, potassium is lost, the forces for attraction exceed the repelling coulombic forces, and the two proteins come together, discharge, and fold Thus, the muscle fiber contracts The tendency to shorten is decreased by a high intracellular potassium concentration, as has been shown to exist in the muscle of the failing heart On the other hand, strong contractions are associated with normal or low intracellular potassium concentrations The active steroid substances, especially digitalis, then, in some way, change the membrane permeability to potassium so that the intracellular concentration of this substance is kept at an ideal level for contraction

You will recall that the resting membrane potential is due primarily to the difference in the concentrations of extra- and intracellular potassium Since Bernstein's[3] suggestion in 1912, this relationship has commonly been expressed in the simple formula shown in Figure 174 This equation describes the theoretical membrane potential, E, as a function of the logarithm of the ratio of intracellular to extracellular potassium, times a constant This ratio is normally about 30 1 which gives a theoretical potential of approximately 90 millivolts This theoretical value has been shown to predict adequately the actual membrane potential over a wide range of conditions

You will also recall that the so-called wave of depolarization occurring with the propagation of an impulse is actually a reversal of membrane potential, that is, the interior of the cell becomes electropositive in relation to the exterior of the cell The

in the membrane potential And just as a gun will
it is loaded, the membrane will not produce an act
until it is charged This results in cardiac arrest, with a
normal internal potassium concentration The actual d it
an experiment using the frog ventricle is seen in the
Brady and Woodbury Figure 176 is our illustration of thei
replotted for emphasis At some point on the falling line of m em
brane potential the energy to fire is no longer sufficient The heart
goes into arrest

This process also explains why occasionally a heart may enter
fibrillation during potassium perfusion If the solution is not
evenly mixed or if the volume is so small that it reaches one
portion of the heart in greater concentration than another the
situation will develop that some areas are in a state of arrest

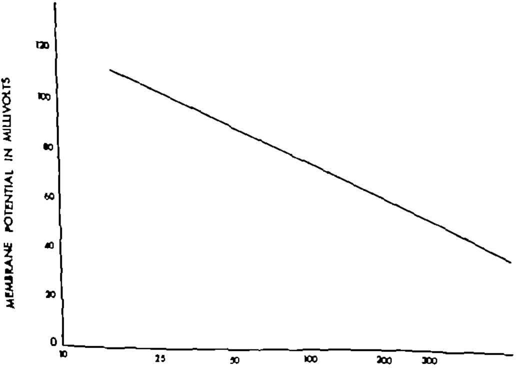


FIG 176 As extracellular potassium increases the resting potential of the membrane falls At some point on this line it will become inadequate to initiate fiber contraction (Modified Brady and Woodbury).

the intracellular potassium is also increased, but not proportionately For example, doubling the external concentration does not double the internal concentration Rather, the change is additive When the external media contains no potassium, there are about 90 mEq/L in the intracellular space And when the external media contains 200 mEq/L, the internal concentration is 290 Since the gain of potassium inside the fiber is a simple linear function of external concentration it is apparent that the intracellular extracellular ratio will decrease rapidly with the addition of extracellular potassium Obviously, thinking back to the Bernstein hypothesis, as the ratio decreases there will be a rapid fall

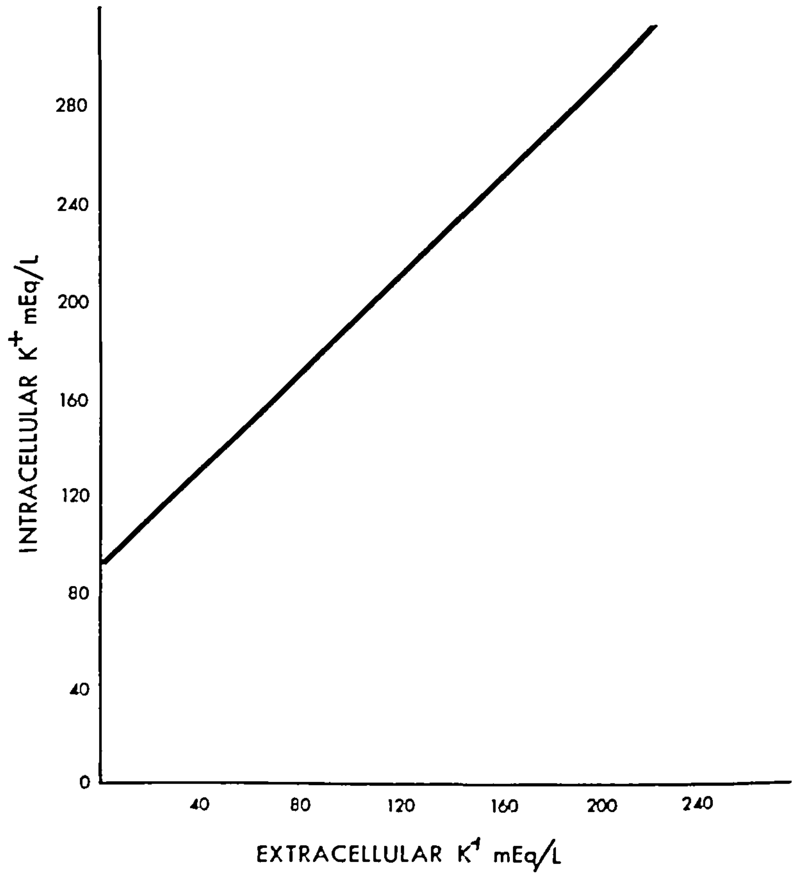


FIG 175 The effect on intracellular potassium concentration of increasing the extracellular concentration of striated muscle (From Boyle and Conway) Note that the effect is additive and that the intracellular increase is therefore not proportional to the extracellular increase

of action were sufficiently great Usually however the period of difficulty in starting post arrest hearts is short and brief periods of additional perfusion with the pump oxygenator will aid in speeding the readjustment I would like to suggest nevertheless that someone should investigate the value of preoperative digitalization with the thought that the pharmacological action of the drug would be present at the time of resumption of beat following potassium arrest We do not know whether stopping the digitalized heart with potassium would be easier or more difficult although we do know that increasing the potassium concentration tends to vitiate the effectiveness of digitalis action Nonetheless it seems reasonable at least in theory that the potassium poisoned digitalized heart should recover its normal contractions more quickly than when undigitalized

As regards the sympathomimetic agents for strengthening weak cardiac contractions their basic mode of action is essentially unknown It is to be remembered also that at least a group of them are not without a specific effect upon the irritability of the myocardium They are in short fibrillatory agents Meek[9] has shown that this effect is specific for the di hydroxy grouping in the 3 4 positions on the catechol amine ring Figure 177 (modified from Meek) illustrates this grouping Unfortunately those agents not having this grouping are primarily vaso constrictors and do not possess the cardiac effects of speeding the rate and strengthening the contraction In addition the catechol amines cause a considerable increase in myocardial oxygen consumption an effect not necessarily desirable in the immediate post surgical heart The use of adrenalin in the treatment of arrest, of weak myocardial contraction and of fine fibrillation must remain empirical until a better understanding of the mode of action of these drugs is achieved It will be of interest to hear the opinions of the subsequent speakers on the role of sympathomimetic drugs in the treatment of hearts arrested by potassium or by acetylcholine

We would like now to return to consideration of the phenomenon of depolarization which triggers myocardial contraction It is now agreed that acetylcholine is essential in fact is uniquely involved in the amazing change in the membrane permeability The overwhelming evidence accumulated by Nachmansohn[10] and

while others are still capable of depolarization. The uniform nature of contraction is destroyed and coarse fibrillation may ensue. The prevention of such fibrillation is to perfuse the myocardium in such fashion that the distribution of the potassium will be even throughout. The treatment is to give more potassium to complete the paralysis.

We have all seen that when the circulation is restored following potassium induced arrest, the contraction may be very weak and ineffective. No doubt this is due to the excess intracellular potassium which produces a wider separation of the contractile proteins and thus a decreased tendency for them to come together and contract. We must wait for the intracellular potassium concentration to be restored to normal in order to bring about an effective beat.

It is possible that one or more agents might be helpful in speeding this escape of potassium. For example, Ringer[6] in 1883, made the following statement:

> Calcium bicarbonate or calcium chloride in physiological doses, or even in smaller quantities than are present in the blood, restore good contractions even when contractility has been lost for seven or eight minutes, and the ventricle no longer responds to strong induction shocks. . . . I conclude, therefore, that a lime salt is necessary for the maintenance of muscular contractility. . . . But whilst calcium salts are necessary for the proper contraction of the heart, yet if unantagonized by potassium salts, the beats would become so broad and diastolic dilatation so prolonged that much fusion of the beats would occur and the ventricle would be thrown into a state of tetanus. . . . If these two salts are not present in the correct proportions, then the trace becomes abnormal.

Thus for years, it has been known that calcium is a good antidote for potassium poisoning. However, as Ringer said, and as Winkler[8] proved in 1940, excessive calcium levels will produce ventricular fibrillation in about 50 per cent of the cases, when the extracellular concentration approaches 24 mEq/L. The agent, therefore, must be used with considerable caution.

In this connection, we can recall the mode of action of digitalis, and consider its ability to decrease the intracellular potassium concentration. This agent might be of considerable value, if its speed

of action were sufficiently great Usually however the period of difficulty in starting post arrest hearts is short and brief periods of additional perfusion with the pump oxygenator will aid in speeding the readjustment I would like to suggest nevertheless that someone should investigate the value of preoperative digitalization with the thought that the pharmacological action of the drug would be present at the time of resumption of beat following potassium arrest We do not know whether stopping the digitalized heart with potassium would be easier or more difficult although we do know that increasing the potassium concentration tends to vitiate the effectiveness of digitalis action Nonetheless it seems reasonable at least in theory that the potassium poisoned digitalized heart should recover its normal contractions more quickly than when undigitalized

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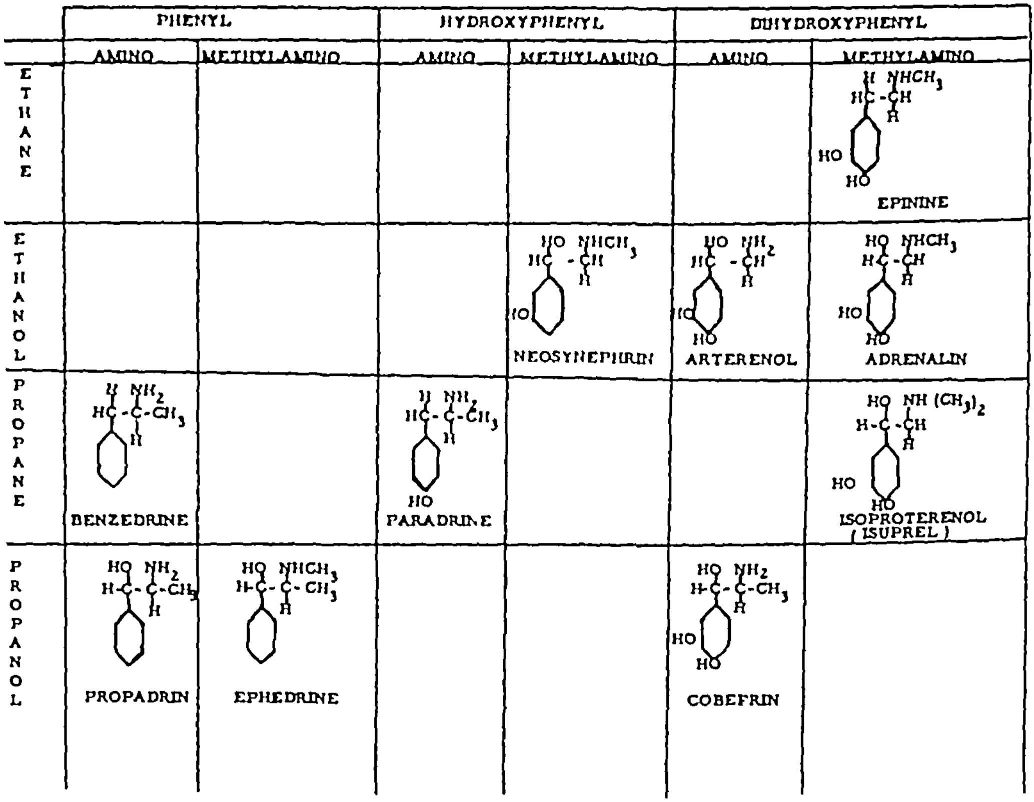


FIG 177 The chemical formulas of some commonly used catechol amines (Modified Meek)

his group has caused even the electro-physiologists to concede acetylcholine an essential role in this process

Moreover, it has been suggested that acetylcholine may even be the agent which endows the heart with its capacity for automaticity We are all aware of the fact that this is an intrinsic property of myocardial tissue and that area which is rhythmically depolarizing at the most rapid rate is the pacemaker for the whole heart The pacemaker is normally the S-A node Before attempting to discuss the important question of how the pacemaker is initially depolarized, let us consider for a moment what is known about the initiation of the contraction of striated muscle Here stimulation of the nerve causes a release of acetylcholine, probably from its bound state, at the myoneural junction The acetylcholine, in turn, depolarizes the end plate, giving rise to the so-called end plate potential When the end plate potential reaches a certain critical level, the adjacent muscle membrane is depolarized, a

self propagating impulse passes over the muscle fiber and contraction results

Cardiac muscle too has a high concentration of bound acetylcholine and acetylcholine is released when the vagus nerve is stimulated but the difficulty in assigning to acetylcholine the role of stimulator of the heart as we can for striated muscle lies in the well known fact that in the mammal stimulation of the vagus or administration of acetylcholine results in cardiac slowing or indeed arrest

Burn and co-workers[11] have made observations which help to reconcile this paradox While investigating the pharmacologic effects of paludrine an antimalarial drug similar to quinine or quinidine they noted that this agent caused slowing of the auricles of the rabbit but more importantly that as the slowing progressed the action of acetylcholine was changed from inhibitory to stimulatory Later they allowed the auricles bathed in oxygenated Tyrode s solution to beat to exhaustion Contractions ceased in this preparation in from twenty four to thirty six hours After cessation of all contractions addition of acetylcholine restored a spontaneous beat Then after a good rhythm had been resumed further addition of acetylcholine caused cardiac slowing In addition the rate of synthesis of acetylcholine by the auricular muscles which fell during the exhaustion period returned to normal following acetylcholine administration

From these studies Burn suggested that acetylcholine in the exhausted auricles is decreased to a level which will not allow spontaneous contractions as evidenced by the low rate of synthesis of acetylcholine in the exhausted auricles Addition of acetylcholine at this point restores spontaneous contractions and at the same time restores the rate of synthesis of acetylcholine toward control levels This experimental relationship is graphically presented in Figure 178 in which auricular activity is plotted against acetylcholine concentration in arbitrary theoretical units In the normal physiologic range of activity the acetylcholine concentration in the tissues would be represented as that part of the abscissa lying under the segment AB on the curve In this range an addition of acetylcholine causes a decrease in auricular activity However when the acetylcholine tissue concentration de

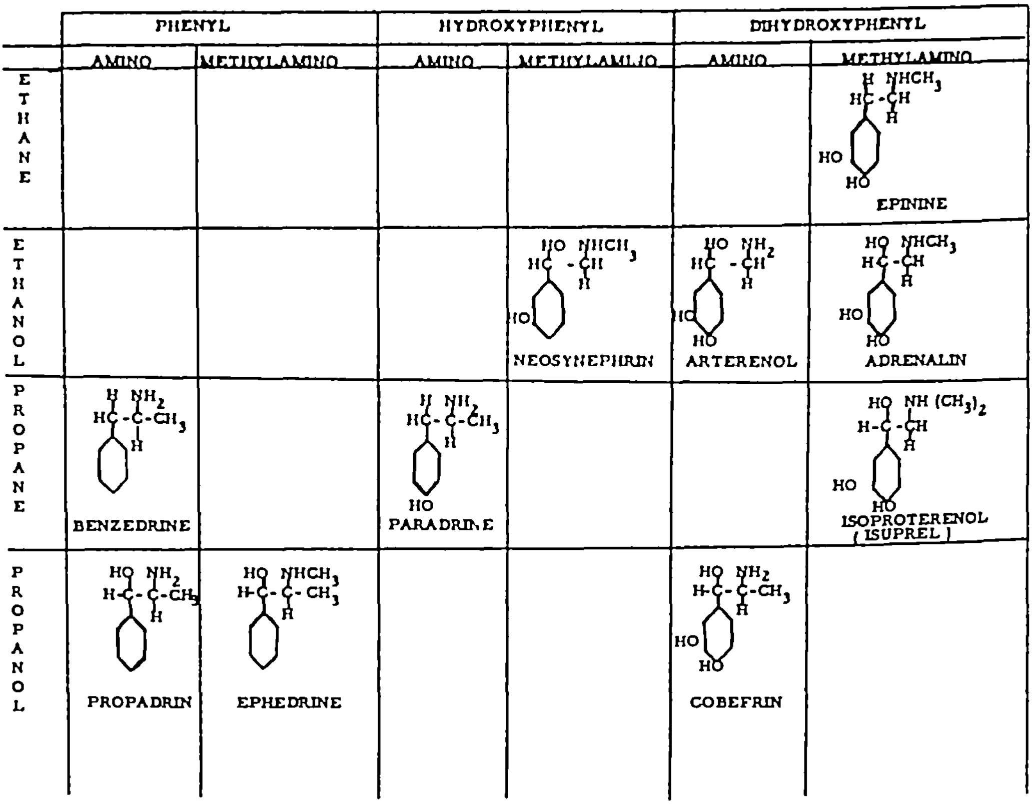


FIG 177 The chemical formulas of some commonly used catechol amines (Modified Meek)

his group has caused even the electro-physiologists to concede acetylcholine an essential role in this process

Moreover, it has been suggested that acetylcholine may even be the agent which endows the heart with its capacity for automaticity We are all aware of the fact that this is an intrinsic property of myocardial tissue and that area which is rhythmically depolarizing at the most rapid rate is the pacemaker for the whole heart The pacemaker is normally the S-A node Before attempting to discuss the important question of how the pacemaker is initially depolarized, let us consider for a moment what is known about the initiation of the contraction of striated muscle Here stimulation of the nerve causes a release of acetylcholine, probably from its bound state, at the myoneural junction The acetylcholine, in turn, depolarizes the end plate, giving rise to the so-called end plate potential When the end plate potential reaches a certain critical level, the adjacent muscle membrane is depolarized, a

have a relationship as described in Figure 180 This graph is from the report of Alles and Hawes[11] As you will recall the enzyme acetylcholine esterase has the function of hydrolyzing acetyl choline to acetic acid and choline If the activity of this enzyme is plotted against increasing acetylcholine concentrations it is found that there is an increase in activity with an increase in con

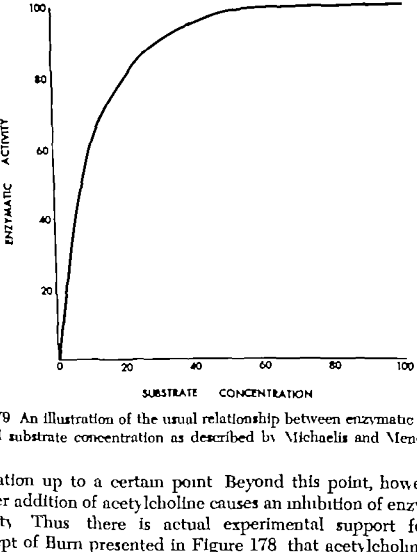


FIG 179 An illustration of the usual relationship between enzymatic activity and substrate concentration as described by Michaelis and Menden.

centration up to a certain point Beyond this point, however a further addition of acetylcholine causes an inhibition of enzymatic activity Thus there is actual experimental support for the concept of Burn presented in Figure 178 that acetylcholine may be both a stimulant and a depressant of myocardial action depending on the level of tissue concentration of the agent at the time of its administration

The importance which these data play in establishing dose levels for specific cardiac effects of acetylcholine is obvious How

creases below point A, for example to point C, there is a diminution of auricular activity At this time, addition of acetylcholine stimulates auricular activity until again point A is reached, after which further acetylcholine would again exhibit an inhibitory action

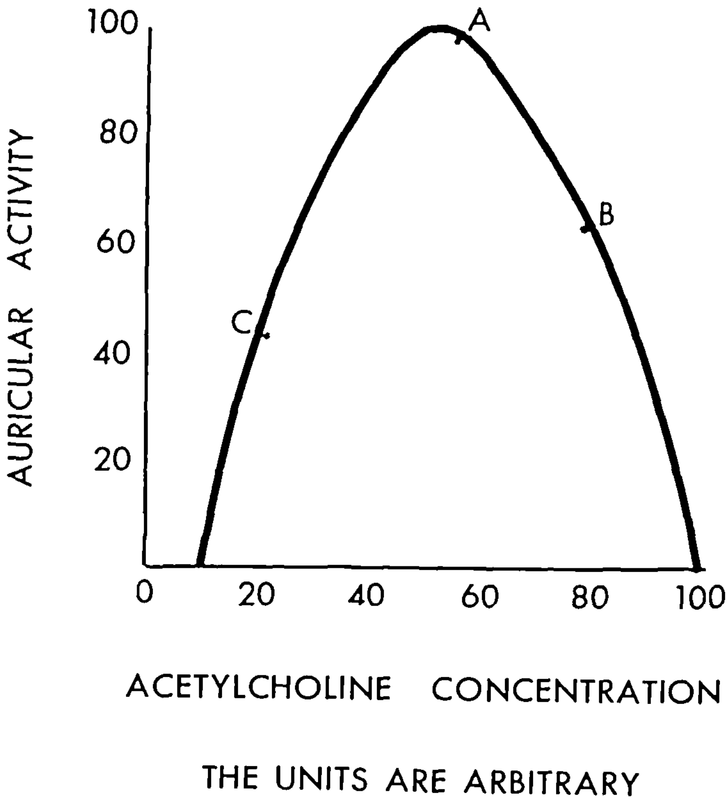


FIG 178 Diagrammatic representation of the effect of acetylcholine concentration on auricular activity (an interpretation of the data of Burn)

This graph is quite unlike most others which demonstrate the effect of substrate concentration on enzymatic activity Figure 179 depicts the usual configuration of such a relationship This is based on the Michaelis-Menten formula [12] With an increase in substrate concentration there is an increase in enzymatic activity up to a plateau beyond which further increases in substrate concentration produce no effect on enzymatic activity However, this equation holds true only for those reactions in which there is a single point of attachment between the substrate and the protein enzyme If there is a two-point attachment of the substrate, we

of commonly accepted opinion concerning the metabolism of this substance

As one molecule of glucose is broken down anaerobically to two molecules of pyruvate two molecules of adenosinetriphos phate are formed The pyruvate is then broken down aerobically through the citric acid cycle to CO_2 and water This process

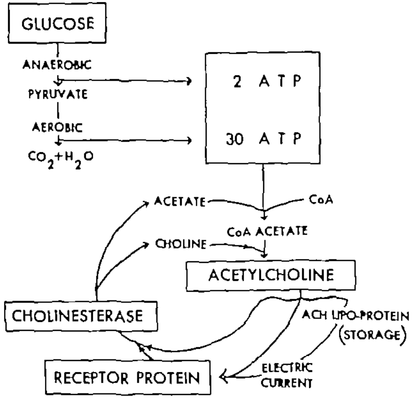


FIG. 181 A simplified diagrammatic representation of some aspects of metabolic acetylcholine

yields 30 molecules of ATP The ATP then serves as the energy source for the linkage of acetate to coenzyme A, from whence the acetate is transferred to choline by the enzyme choline ace tylase—thus forming acetylcholine The latter is then either stored in the form of a lipo-protein complex or acts immediately on the receptor site Free acetylcholine is very rapidly hydrolyzed by the enzyme choline esterase

From work in our own laboratory we feel that this cycle is of practical use in the prevention of ventricular fibrillation. We have shown that continuous coronary perfusion of acetylcholine inhibits

ever, one can say that no matter what the existing level of concentration, if enough acetylcholine is added to the system, depression of cardiac activity will occur. This dose, moreover, will need to be very large indeed if blood is used as the perfusion vehicle because plasma and red cells both contain acetylcholine-splitting enzymes. The dose will be less if Ringer's solution is used. For cardiac arrest, the amount to be given, then, will be large, and can

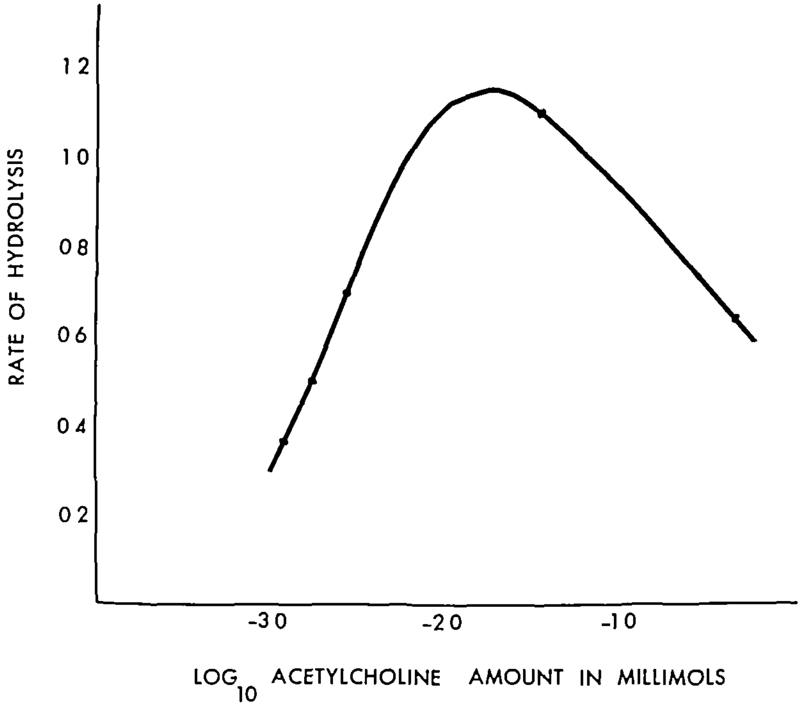


FIG. 180. Actual data on the relationship between acetylcholine concentration and acetylcholine esterase activity (from Alles and Hawes).

be simply described as "enough to stop the heart." As with potassium, it is important to be sure that the agent is evenly distributed throughout the myocardium.

It is obvious from the discussion to this point that acetylcholine is an extremely important substrate in myocardial function, relating as it does to automaticity, to transmission of impulse at the synapse, and to conduction of the depolarization wave along the muscle fiber. The metabolism of this substance is, therefore, of great interest in further understanding such events as cardiac arrest or fibrillation. Figure 181 is a somewhat simplified version

of commonly accepted opinion concerning the metabolism of this substance

As one molecule of glucose is broken down anaerobically to two molecules of pyruvate two molecules of adenosinetriphosphate are formed The pyruvate is then broken down aerobically through the citric acid cycle to CO_2 and water This process

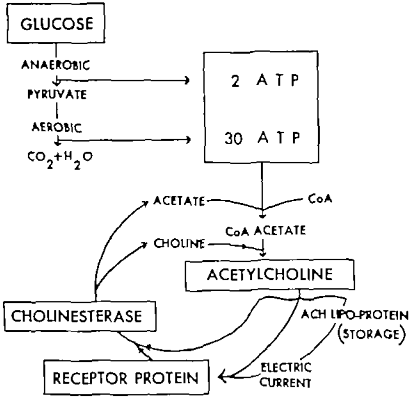


FIG 181 A simplified diagrammatic representation of some aspects of metabolic acetylcholine

yields 30 molecules of ATP The ATP then serves as the energy source for the linkage of acetate to coenzyme A from whence the acetate is transferred to choline by the enzyme choline acetylase—thus forming acetylcholine The latter is then either stored in the form of a lipo-protein complex or acts immediately on the receptor site Free acetylcholine is very rapidly hydrolyzed by the enzyme choline esterase

From work in our own laboratory we feel that this cycle is of practical use in the prevention of ventricular fibrillation We have shown that continuous coronary perfusion of acetylcholine inhibits

ventricular fibrillation in the hypothermic dog undergoing cardiac surgery [11] Moreover, release of endogenous acetylcholine by electrical stimulation of the peripheral stump of the vagus nerve will also inhibit ventricular fibrillation In addition, we have shown that inhibition of the choline-esterase enzyme by neostigmine inhibits ventricular fibrillation presumably by allowing an accumulation of acetylcholine We have noted, further, that the duration of the anti-fibrillatory action of neostigmine is much less if no coronary blood flow is allowed [15] This is certainly reasonable, in view of the inefficient synthesis of ATP under anaerobic conditions We have also found that continuous coronary perfusion of ATP also has an anti-fibrillatory effect [16] More recently, we have shown that intravenous administration of glucose, fat, or glycine during hypothermia also reduces the incidence of ventricular fibrillation [17] As is well known, amino acids or fat can enter freely the myocardial metabolic cycle And, finally, we have shown that a single coronary injection of bethanechol (Urecholine[Rx]) will prevent ventricular fibrillation for long periods with or without coronary blood flow [15] Since this acetylcholine-like agent is not hydrolyzed by cholinesterase, presumably it continues to act on the receptor site until removed There is no doubt that there is a relationship between the metabolic cycle of acetylcholine and cardiac arrhythmias, and that this relationship can be used for practical purposes in the control of ventricular fibrillation

Acetylcholine, then, is a fundamental metabolite which can cause cardiac arrest It is a common experience, however, to have periods of weak heart beat or even occasionally fibrillation during the period of restoration of coronary circulation following such arrest It would be desirable to have the necessary knowledge to allow one to select intelligently suitable antidotes, such as atropine or the sympathomimetic agents Atropine at the moment, appears to be the most rational Its action is thought to be due to its competitive relationship to acetylcholine in seeking the same receptor sites It is, in effect, an acetylcholine blocking agent Indeed, atropine has been shown in large doses to be a ganglionic blocking agent Moreover, in our laboratory, we have reversed the cardiac arrest of bethanacol by the use of this agent Since its

action is not through any alteration in basic metabolic cycles, it has a margin of safety which serves to recommend it to our use

In summary then we have briefly reviewed some of the aspects of myocardial function and metabolism and a few agents which effect these processes We must conclude by offering our apologies that this discussion was not presented to you by someone with more experience and training in the field of pharmaco dynamics However it is our feeling that the clinical application of basic knowledge in the field of cardiac surgery is as pertinent as it is everywhere else in the practice of medicine

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ACETYLCHOLINE INDUCED ASYSTOLE

An Adjunct in Open Heart Operations with Extracorporeal Circulation

By

CONRAD R LAM, M D., THOMAS GAHAGAN, M.D , CHARLES SERGEANT, M D , *and* EDWARD GREEN, M.D

THE POSSIBILITY that some form of drug induced cardioplegia might be of value in cardiac surgical procedures was investigated in our laboratory in the latter part of the year 1952 A report[1] to the Michigan Heart Association dated January 15 1953 contained the following paragraph

"*An Investigation of the Value of Stopping the Heart for Intracardiac Operations* A solution of potassium chloride has been used to cause an immediate cardiac arrest The token operation is carried out, after which the heart is started by massage electrical defibrillation, calcium salts and cardiac stimulants as necessary This technic has been used in operations of four minutes duration in which the right side of the heart has been opened. The last five consecutive animals in the series have survived for one month or more with no residuals Operations with the heart asystolac for ten minutes have been done with the aid of cerebral cross transfusion with a donor animal A study is now in progress to compare the likelihood of recovery of hearts treated in this way with those rendered bloodless by simple vena cava occlusion " The study went on to include a large number of experimental cardiac arrests with the brain protected by hypothermia rather than with cross circulation and was reported in 1955 before the American Association for Thoracic Surgery [2]

From the Division of Thoracic Surgery of the Henry Ford Hospital, Detroit, Michigan

The experimental work was supported by a grant from the Michigan Heart Association.

The method used to stop the heart in these early experiments was the injection of a solution of potassium chloride into the left ventricle. Obviously, the amount of the drug which entered the coronary arteries was unpredictable and its distribution was uneven, since the final phases of perfusion were dependent on the failing heart action which was reinforced by manual systole. Likewise, the method of resuscitation was relatively crude, consisting of manual systole performed to provide blood flow through the coronary arteries. The drugged muscle fibers became resuscitated at different times, and ventricular fibrillation was practically inevitable. In nineteen of twenty animals in one series, however, electrical defibrillation was successful in restoring an effective beat.

In the early search for a cardioplegic agent, acetylcholine had been considered, but was not tried immediately because Bjork[3] had reported that no effective arrest could be produced with it. In the fall of 1955, we decided to reinvestigate the possibilities of acetylcholine. It worked very well, as can be seen from the following paragraph from the research report to the Michigan Heart Association[4] dated Jan. 14, 1956.

"Because of the disadvantages of potassium-induced cardiac standstill, which is nearly always complicated with ventricular fibrillation during the period of resuscitation, we have investigated the possible advantages of acetylcholine as an 'anesthetic agent' for the heart. In acute experiments, this appeared to be an ideal method. With the aorta occluded just distal to the coronary ostia, a solution of acetylcholine was injected into the aorta and thence into the coronary arteries. There was immediate cessation of the heartbeat. After a variable period of time, heparinized whole blood was perfused through the coronary system and the heartbeat reappeared spontaneously."

It was natural that the reservoir of heparinized blood was soon replaced by a pump-oxygenator which not only provided an inexhaustible supply of oxygenated blood for resuscitation of the heart, but also gave protection to the brain and other parts of the body during the cardiac by-pass. The pump-oxygenator which we first used and continue to use is that of the bubble type devised by Lillehei, DeWall and their associates.[5] Since April 4, 1956, the combination of extracorporeal circulation and induced cardiac

arrest has been used in the surgical treatment of 112 patients

The advantages of cardiac standstill during intracardiac operations are obvious During the conventional by pass of the heart with the pump-oxygenator with the heart beating there is a continuous flow of blood from the coronary sinus which may obscure the operating field in the ventricle or atrium even though attempts are made to remove the blood by aspiration If the by pass is for a considerable period of time it is mandatory that the aspirated blood be returned to the system A certain amount of hemolysis or other trauma to the blood is produced by this manipulation In the open beating heart there is danger of air embolism to important systemic arteries Naturally some of the surgical procedures can be carried out with greater accuracy if the field is quiet as well as dry

The method of inducing asystole which we have adopted is illustrated in Figure 182. After the introduction of the appropriate cannulae into the subclavian artery and the venae cavae they are attached to the pump-oxygenator and the pump is started The snares about the vena caval cannulae are tightened If the check on the level of the blood in the helix of the oxygenator system shows that inflow and outflow rates are equal we proceed to stop the heart A non-crushing clamp is placed across both the aorta and pulmonary artery It is not necessary to spend time dissecting the two great vessels apart Acetylcholine in the amount of 10 mg per kilo of body weight is injected into the aorta proximal to the clamp The commercial preparation of acetylcholine which we have used is Acecholine manufactured by the Anglo-French Laboratories and available in the U S from E Fougera & Co of New York. Enough physiological saline solution is added to make the volume of injection about 20 cc The injection is made into the aorta through a small figure-of-eight suture which is tied as soon as the needle is removed

The heart stops when about two-thirds of the solution has been injected but the injection is continued until the calculated dose has been given A second syringe containing a similar amount of acetylcholine is in readiness and can be used if a technical error has resulted in the loss of some of the solution in the first syringe Although apparently in arrest, the heart beats when the ventricu

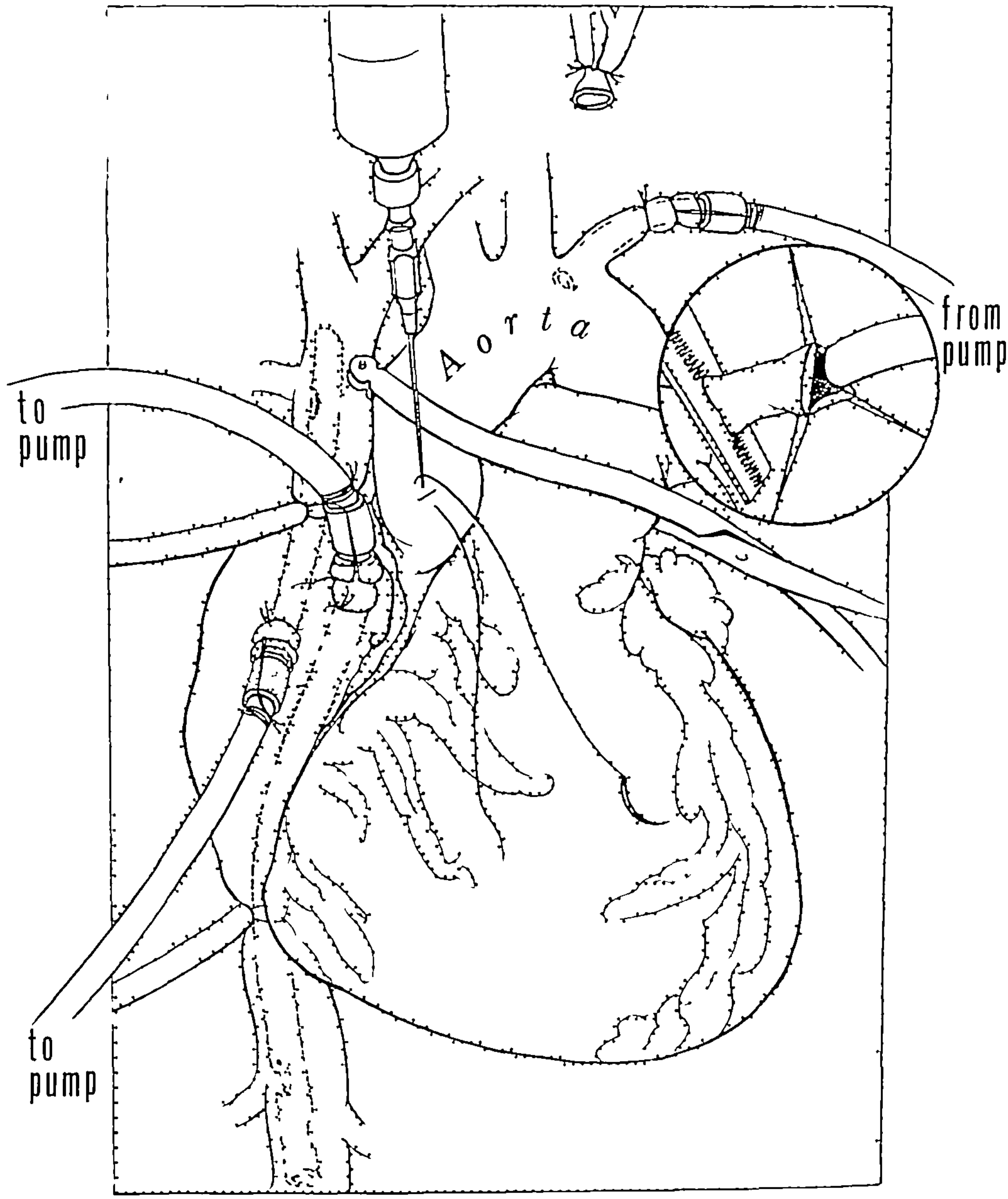


FIG 182 Drawing illustrating cannulations for attachment of the pump-oxygenator for extracorporeal circulation, and method of inducing cardiac arrest by the injection of acetylcholine into the aorta

lar wall is stimulated mechanically by forceps or needles There is usually no activity during the suture of interventricular septal defects or procedures on the heart valves No additional acetylcholine is given for the sporadic beats which arise as a result of direct stimulation

To resuscitate the heart, one has simply to remove the clamp

from the aorta This permits the blood from the oxygenator to flow into the coronary arteries The cardioplegic drug is washed out of the arteries into the coronary veins where it escapes into the right atrium via the coronary sinus During the repair of an interventricular septal defect there is of course an incision in the right ventricle from which the blood containing the drug can escape In operations for atrio ventricularis communis etc egress for this blood is provided by the right atrial incision It has been our policy to remove the aortic clamp before beginning the sutur

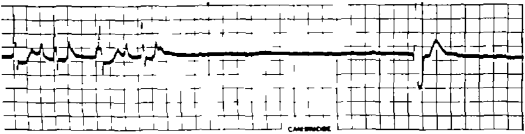


FIG 183 Electrocardiogram recorded at the instant of the injection of acetylcholine Note the prompt arrest and one beat occurring later probably the result of the ventricular incision Patient was five years old, with fistula between left ventricle and right atrium successfully closed

ing of the cardiotomy incisions The suture line can be put in easily during the resumption of the heart beat and the cardiac contractions occurring during the final stages of the closure insure against air being trapped It would appear to be a good idea to permit the heart to beat against no resistance like an idling motor until good rhythm has been established.

In Figure 183 is reproduced the electrocardiographic tracing at the instant of arrest with acetylcholine The rapid resumption of a normal electrocardiographic pattern as seen in a typical case is illustrated in Figure 184

CLINICAL EXPERIENCE WITH INDUCED CARDIAC ARREST

Of the 112 operations in which elective asystole has been employed in conjunction with the pump-oxygenator seventy two were for the repair of interventricular septal defects in seventy one patients (one patient had a second operation for the repair of a recurrence of the defect) The technical details of these operations

have been reported elsewhere [6-9] Induced cardiac arrest has appeared to be especially valuable in the repair of ventricular septal defects In the perfectly dry and quiet field, the sutures can be placed with great accuracy Restoration of the heartbeat has been accomplished readily The heart in one of the early cases, in which there was poor coronary perfusion because of the low flow from the pump-oxygenator, had to be assisted manually Ventricular fibrillation appeared in four hearts (ventricular defect cases) during the resuscitation One of these had fibrillated twice before the pump run, the last cannulae having been put in while the heart was being massaged Sinus rhythm was restored in each case with one light electrical countershock

Atrioventricular block has been encountered with considerable

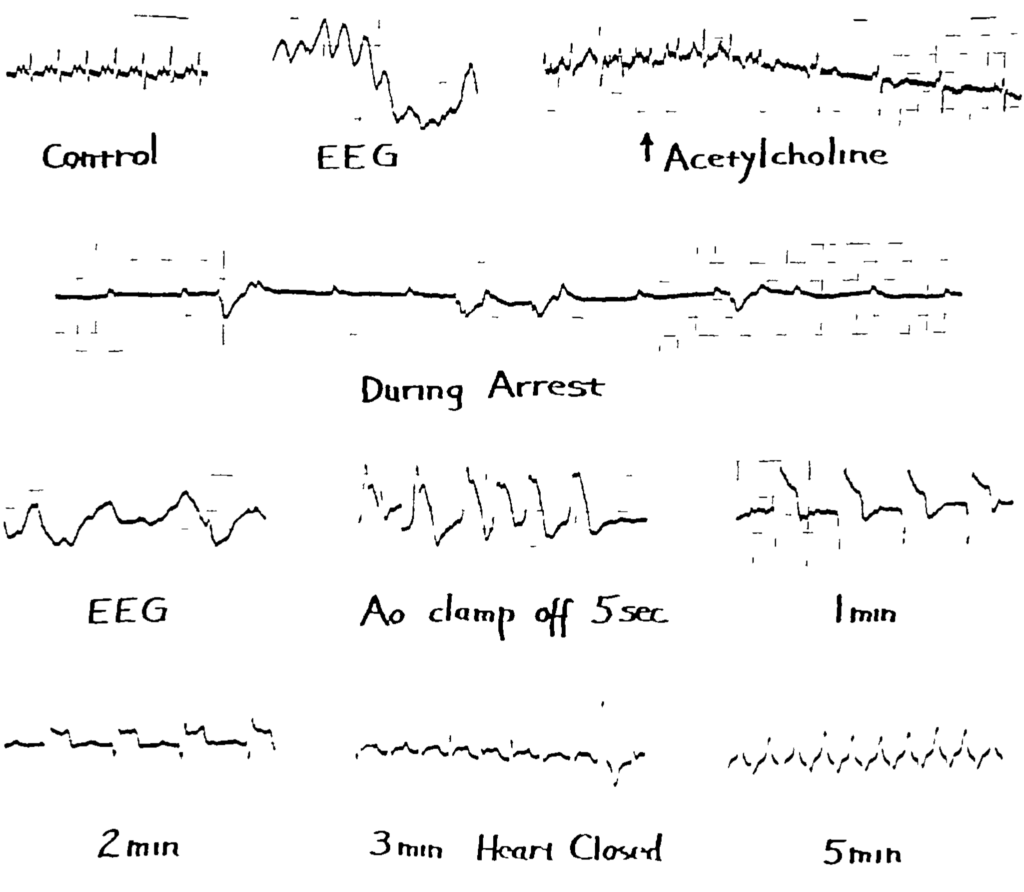


FIG 184 Electrocardiograms and electroencephalograms taken during cardiac by-pass and cardiac arrest in a girl age fifteen months, during repair of ventricular septal defect (Lead II of EKG)

frequency in the septal defect cases and the incidence could be considered as an indictment of the principle of induced cardiac arrest since theoretically an offending suture could be removed as soon as the arrhythmia is noted However it is known that the complication occurs with about the same frequency (10 per cent) in centers where induced arrest is not used

The total mortality in the seventy two operations for the repair of interventricular septal defect has been 32 per cent (23 cases) Most of the fatalities have been in the tiny babies under the age of one year There were three deaths in twenty nine patients over the age of three years and one of these was atypical with marked underdevelopment of the right ventricle

Induced arrest was also used in a miscellaneous group of forty cases Only the complicated interatrial septal defects were repaired by open operation This group includes seven instances of atrioventricularis communis all but one of whom survived the immediate postoperative period There were two late deaths with evidence of recurrence of the defect

Successful operations have been carried out for the removal of atrial myxoma, isolated infundibular stenosis of the right ventricle and anomalous insertion of the veins of the right lung without interatrial septal defect

Surgery of the aortic valve has been attempted in five cases using the open technic with induced cardiac arrest Two patients had congenital aortic stenosis One valve was successfully opened through the aortotomy and the heart was resuscitated In a second case almost intractable ventricular fibrillation occurred, and eventually the patient expired with hemorrhage from the aortic incision and recurrent ventricular fibrillation

Three attempts were made to insert a prosthesis of the watch spring type for aortic insufficiency In no instance was a satisfactory arrest of the heart produced obviously because the acetyl choline which was injected into the aorta did not enter the coronary arteries but passed into the left ventricle through the incompetent valves It is our opinion that induced cardiac arrest has little place in the surgical treatment of aortic lesions because during the resuscitation phase the heart has to work against the pump unless there is an aortotomy and coronary circulation is

maintained by retrograde perfusion through the coronary sinus We have had no experience with the latter method Bailey[11] reports that he has operated on eleven patients with aortic stenosis by the open technic with cardiac by-pass, with only one death.

CONCLUSION

Elective asystole (induced cardiac arrest, cardioplegia) is a valuable and safe adjunct in many kinds of intracardiac surgical procedures carried out with the aid of extracorporeal circulation

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ELECTIVE CARDIAC ARREST WITH POTASSIUM CITRATE

By

DONALD B EFFLER, M D *and* LAURENCE K GROVES, M D

THE ADVANTAGES of cardiac operations under elective cardiac arrest are best summarized by recalling a basic surgical principle The ideal surgical field is well exposed motionless and free of blood In the days before the introduction of open cardiotomy by the by pass technic the surgical field during cardiac operations could not be well visualized—valves were fractured or cut masses of tissue were removed by rongeur and chamber walls were in vaginated in an unsightly fashion to close defects in the interatrial septum At that time such technics were justifiable and indeed courageous but it is folly to apply them to open cardiac surgery when the adjunct of arrest will give an approach to the ideal

In the course of our experimental work on open heart surgery in 1955 we found that the Melrose technic for inducing car diac arrest with potassium citrate was simple easily duplicated in our experimental laboratory and of great technical help in in traventricular operations [1,2] On February 17 1956 for the first time we employed elective cardiac arrest with potassium citrate while closing an interventricular septal defect in a seventeen month-old child [3] The simplicity of the technic and the ideal exposure that it afforded convinced us that if unforeseen compli cations or toxicity did not materialize this adjunct to cardiac sur gery would be a very important advance The Melrose technic now has been employed in 96 patients and the results have given us no cause to employ or to search for other cardioplegic drugs

The specific effect of potassium upon the heart muscle has been well known since the time of Ringer [3] As early as 1929 [4] it was

From the Department of Thoracic Surgery The Cleveland Clinic Foundation and The Frank E Bunts Educational Institute Cleveland Ohio

maintained by retrograde perfusion through the coronary sinus We have had no experience with the latter method Bailey[11] reports that he has operated on eleven patients with aortic stenosis by the open technic with cardiac by-pass, with only one death

CONCLUSION

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beat weakens the heart appears to dilate as the muscle fibers relax Usually the ventricles are paralyzed first the atrial appendages are affected last because they are the most peripheral portion of the coronary circulation

Originally the potassium citrate–blood mixture contained 2 ml of 25% potassium citrate mixed with 18 ml of heparinized blood taken from the pump reservoir We have since found that one-half the amount or 1 ml of 25% potassium citrate mixed in 19 ml. of heparinized blood is equally effective in small hearts The surgical nurse prepares the mixture immediately before use and it is placed in a battery of 20-cc. syringes to expedite injection For a patient less than five years of age the contents of one syringe usually are adequate however the dose of potassium citrate–blood mixture for any patient is that amount required to induce complete cardiac arrest as determined by visual examination and by electrocardiographic monitoring The danger of potassium citrate overdosage appears to be negligible

The quiescent heart may be opened through any chamber the surgeon elects Most frequently it will be the right ventricle or the right atrium or both As the blood is removed from the chamber by an aspirator the field can be carefully inspected without fear of a time limit or of an arrhythmia being produced by manipulation If a defect is present in the ventricular or the atrial septum there will be a continuous flow of blood from the left heart caused by the bronchial circulation and any collaterals that may be present As the defect is closed this blood may appear as a retrograde flow from the pulmonary artery If an unsuspected defect is present, the flow should appear at the site of that defect It must be remembered, however that closure of defects may be followed by spontaneous resumption of the heartbeat as the pressure slowly builds in the left heart to the point that it will gradually flush the potassium through the coronary circulation Usually this spontaneous resumption is of little significance because the surgeon is ready to terminate the procedure Distention of the left side of the heart by collateral circulation in addition to restarting the heart, is undesirable because of consequent vascular engorgement of the lungs For this reason the pulmonary artery should be left open as a vent and septal defects should not be

suggested that potassium chloride could be used clinically in the treatment of severe ventricular arrhythmias, and we have no doubts that it has been used many times in experimental surgery in efforts to control ventricular fibrillation. Our observations in the laboratory and of the ninety-six patients in whom potassium citrate has been used to induce cardiac arrest, have convinced us that the effect of potassium citrate on the myocardium is transient and nontoxic. It would appear that the myocardial paralysis induced by the potassium inhibits the metabolism of the muscle fiber and greatly reduces its oxygen need. It is likewise apparent that the bond between the paralyzed muscle and the potassium is tenuous and easily severed by the simple expedient of perfusing the coronary circulation with oxygenated blood. (One of our patients, a fifty-five-year-old man, had an uneventful recovery after cardiac arrest of fifty-eight minutes' duration.) The physicochemical mechanism by which the heart stops and restarts is by no means understood, but it appears constant in human and canine hearts, either in health or disease.

Technic. A virtue of the Melrose technic for elective cardiac arrest is its simplicity: not only is the potassium citrate easily administered and its effect easily terminated, but no additional drugs are required for antagonistic effects. After the patient has been connected to the pump-oxygenator and a satisfactory flow rate of blood through the machine has been established, caval ligatures are secured to complete the by-pass of the heart. When the by-pass has been completed, the mean arterial pressure should be higher than 60 mm Hg (measured by an intra-arterial cannula) and there should be significant decompression of the right heart. Although after by-pass the heart is appreciably smaller and its output markedly less than normal, there still is a significant return of blood via the coronary sinus and bronchial pathways to the by-passed heart. This flow is increased considerably when there is extensive collateral circulation, such as occurs in patients having tetralogy of Fallot. The aorta is cross-clamped about 2 to 3 cm distal to its valve, and the potassium citrate–blood mixture is injected into the proximal occluded segment until asystole is complete. The mixture is injected quickly through a 22-gauge needle on which a sleeve controls the depth of penetration. As the heart

beat weakens the heart appears to dilate as the muscle fibers relax. Usually the ventricles are paralyzed first, the atrial appendages are affected last because they are the most peripheral portion of the coronary circulation.

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The quiescent heart may be opened through any chamber the surgeon elects. Most frequently it will be the right ventricle or the right atrium or both. As the blood is removed from the chamber by an aspirator, the field can be carefully inspected without fear of a time limit or of an arrhythmia being produced by manipulation. If a defect is present in the ventricular or the atrial septum, there will be a continuous flow of blood from the left heart caused by the bronchial circulation and any collaterals that may be present. As the defect is closed, this blood may appear as a retrograde flow from the pulmonary artery. If an unsuspected defect is present, the flow should appear at the site of that defect. It must be remembered, however, that closure of defects may be followed by spontaneous resumption of the heartbeat as the pressure slowly builds in the left heart to the point that it will gradually flush the potassium through the coronary circulation. Usually this spontaneous resumption is of little significance because the surgeon is ready to terminate the procedure. Distention of the left side of the heart by collateral circulation, in addition to restarting the heart, is undesirable because of consequent vascular engorgement of the lungs. For this reason the pulmonary artery should be left open as a vent and septal defects should not be

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probably occurs much more frequently during open heart operations than is generally realized and it is of relatively little significance

Cardiac arrest techniques that involve cross-clamping the aorta emphasize the frequency of this complication because all air is trapped proximal to the aortic clamp This portion of the aorta is uppermost, and on the removal of the clamp the air moves backward with the retrograde perfusion and must eventually be dissolved or enter the coronary ostia particularly the anteriorly situated right one As has been mentioned it is not infrequent to see a number of small bubbles course through the coronaries when the aortic clamp is first removed With the high flow rates now in use significant delay in resumption of heartbeat or significant arrhythmias rarely occur in these cases If difficulties do ensue perfusion rates should be increased as much as feasible and subsequently electric shock used as indicated We are unaware of any instance in which air embolism of this type has resulted in more than temporary discomfiture to the operating team

In general a delay in starting of the quiescent heart is most commonly explained by inadequate myocardial perfusion this in turn may be produced by air emboli improperly placed arterial cannula or too low rate of flow of oxygenated blood from the pump-oxygenator Experience with varying rates of perfusion has clearly demonstrated the advantages of the high rates the heart starts far more rapidly the incidence of arrhythmia is greatly reduced, and the postoperative course is smoother with less metabolic acidosis

Probably the most significant factor in lowering operative morbidity and mortality in our series of cases has been the increase in rates of perfusion to levels much greater than those dictated by the "azygos flow principle" We now use flow rates of from 70 to 100 ml per kilogram of body weight per minute which usually give "on the run" mean blood pressures of from 60 to 100 mm Hg These increased rates of flow have resulted in a marked acceleration in the restarting of the arrested heart and a reduction in postarrest arrhythmias Now vigorous contractions are almost always apparent within one minute after the aorta has been un

closed until all other intracardiac work, such as excision of infundibular muscle, has been accomplished

Restarting the quiescent heart is even simpler than arresting it When the intracardiac procedure has been completed, the initial incision may be closed entirely or in part If the incision is closed entirely, every effort should be made to remove all air from the chambers or major vessels The occluding clamp then is removed from the aorta and as the coronary circulation is resumed by the perfusion apparatus, the potassium citrate–blood mixture is washed from the myocardium and escapes into the right side of the heart by way of the coronary sinus and Thebesian veins It is our practice to allow the blood that is first returned to overflow through the partially closed incision and, as the heart spontaneously resumes its beat, to complete the closure As stated previously, the bond between the potassium electrolyte and the paralyzed muscle is extremely tenuous and is rapidly dissolved by adequate perfusion of the heart by oxygen-saturated blood from the pump-oxygenator In the majority of instances the heart resumes an effective beat within one minute after that perfusion, and is capable of maintaining a satisfactory pressure within five to ten minutes after contractions are restored None of our patients has had a significant postoperative rise in serum potassium values or any untoward systemic effects from the doses used

Avoidance of Complications. If the perfusion of oxygen-saturated blood from the pump-oxygenator is adequate and proper technique has been utilized, the heart should resume an effective sinus rhythm Significant arrhythmias, particularly ventricular tachycardia or ventricular fibrillation, suggest myocardial anoxia and this complication most frequently results from the presence of air in the coronary circulation Frequently, this air can be seen as bubbles in the radicles of the coronary vessels and is associated with a patchy discoloration of the myocardium The maintenance of a satisfactorily high flow of oxygenated blood will cause the air to pass on rapidly and the color of the myocardium to improve steadily It is usual for ventricular tachycardia or fibrillation to convert spontaneously to a sinus rhythm when proper myocardial oxygenation is re-established Minor air embolism into the aorta

first one hundred and fifteen patients It is not a standard procedure for correction of valvular pulmonary stenosis and ostium secundum defects of the auricular septum

Experience with both clinical and experimental operations in which elective cardiac arrest by the Melrose technique was employed has failed to demonstrate any undesirable side effects that might be attributed to the potassium citrate or to the manner in which it was used Although we have had misgivings along the way time and further experience so far have vindicated the use of potassium citrate Most of the accidents that have been brought to our attention can be attributed directly to improper use of the technique It must be remembered that elective cardiac arrest is strictly an adjunct to open heart operations if the basic equipment and the resultant perfusion are inadequate the problems will only be compounded by the use of cardiac arrest

In general there are three factors that will help the surgeon to avoid difficulties when cardiac arrest is employed However these factors are important to any type of open heart operation with or without elective cardiac arrest

1 Maintenance of high rates of flow of oxygenated blood from the pump-oxygenator

2 Regulation of body temperature to approximate the normal as closely as possible

3 Prevention of air being trapped in the heart

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1 Kolff W J Effler D B Groves L K Peereboom G Aoyama S and Sones F M., Jr Elective cardiac arrest by the Melrose technic potassium asystole for experimental cardiac surgery *Cleveland Clin Quart* 23 98-104, 1956

2 Effler D B Groves L K Sones F M Jr and Kolff W J Elective cardiac arrest in open heart surgery report of three cases *Cleveland Clin Quart* 23 105-114, 1956

3 Ringer S Further contribution regarding influence of different constituents of blood on contraction of heart *J Physiol* 4 29-42, 1 plate 1883

4 Hooker D R On recovery of heart in electric shock. *Am J Physiol* 91 305-328 1929

clamped. With high flow rates, the incidence of ventricular arrhythmias has been reduced even in patients having coronary air emboli

An additional factor that should be considered in the safe conduct of a patient through this procedure is body temperature. The widely opened chest and the extracorporeal blood circuit both are great potential sites of heat loss Hypothermia in itself has had wide application in cardiac surgery, but it has been our impression that this is an additional cause of myocardial irritation and should be avoided when a pump-oxygenator is used Certainly with the high perfusion rates now used, the addition of hypothermia is not necessary, and this potential source of arrhythmia and reduced cardiac activity constitutes only an additional hazard. We have seen greatly depressed cardiac activity with prolonged low postoperative blood pressures after potassium citrate arrest during which the patient's temperature fell to the low 90's on the Fahrenheit scale Furthermore, such patients tend to show peripheral cyanosis The response to rewarming may be dramatic and, more importantly, the same difficulties will
are taken to avoid low body temperature

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CLINICAL EXPERIENCE WITH RETROGRADE PERFUSION OF THE CORONARY SINUS FOR DIRECT VISION AORTIC VALVE SURGERY WITH OBSERVATIONS UPON USE OF ELECTIVE ASYSTOLE OR TEMPORARY CORONARY ISCHEMIA

By

C. WALTON LILLEHEI, M.D., VINCENT L. GOTT, M.D., ROBERT D. SELLERS, M.D., PAUL C. HODGES, M.D., *and* RICHARD L. VARCO, M.D.

ALMOST TWO YEARS AGO, in this clinic, a thirty-nine year old woman with severe acquired calcific aortic stenosis had a direct vision repair of her diseased valve utilizing a pump-oxygenator in combination with retroperfusion of the coronary sinus [1] This technic allowed for a precise, deliberate plastic repair of the valve while providing the contracting myocardium with oxygenated blood An excellent clinical result was achieved in this patient, and she is living and working as a normal individual at this time. Since that initial case, retrograde perfusion of the coronary sinus has been employed in ten additional patients for a variety of lesions involving the left heart The results of these operations are presented at this time, together with pertinent comparative observations derived from experience in nine other patients with aortic valve dis-

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1 Graduate School, University of Minnesota
2 Minnesota Heart Association
3 Life Insurance Medical Research Fund
4 American Heart Association
5 National Heart Institute, USPHS #830

ease in whom alternative techniques (elective asystole with potassium citrate or acetylcholine temporary coronary ischemia) for direct vision aortic valve surgery have been tested in conjunction with total cardiopulmonary bypass at normal body temperature utilizing the pump-oxygenator

Method of Coronary Sinus Retroperfusion

The patient is connected to the pump-oxygenator (bubble)[3] in the usual manner and the perfusion is begun totally bypassing the heart and lungs The right atrium is opened and an appropriately sized plastic catheter (usually #14F to 16F) with a rigid plastic tip is inserted into the coronary sinus and secured in place with a purse string suture (Figure 185) On the basis of considerable laboratory experience[2] it is believed that the optimal perfus

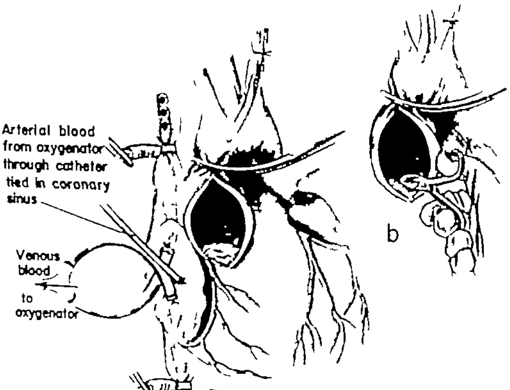


FIG 185 Technic for retroperfusion of the coronary sinus to permit aortotomy with maintenance of the coronary circulation during total cardiopulmonary bypass utilizing extracorporeal circulation

ing pressure for this retrograde coronary sinus flow is a mean of about 35-40 mm Hg We have achieved this perfusion pressure by several technics, but the simplest method has been to perfuse the coronary sinus from a reservoir of oxygenated blood approximately 50 cm above the heart The blood volume in the reservoir is maintained by an inflow of arterial blood from the oxygenator (Figure 186) After starting the retroperfusion the ascending aorta is cross clamped, and if an aortic valvuloplasty is to be performed, the ascending aorta is incised longitudinally The diseased valve is then repaired under direct vision When the valvuloplasty is completed, the aortotomy is reapproximated by application of a suitable vascular clamp and carefully closed with a running silk suture Any residual air within the aorta is expelled by the retrograde flow as the aortotomy is sutured As soon as the aortotomy has been closed, the retroperfusion is terminated and the clamp removed from the aorta, restoring forward coronary perfusion

Recently, we have used acetylcholine-induced asystole in combination with retroperfusion After commencing the perfusion of the coronary sinus, acetylcholine is injected into the retrograde catheter until there is almost a complete standstill The retrograde catheter is then clamped (Figure 186, inset) This technic facilitates the arrest of the heart, and also provides a still, dry field during the few minutes that the valvuloplasty is being performed Before the aortotomy is closed, the clamp is removed from the retrograde catheter This allows arterial blood to wash the acetylcholine from the myocardium and reinstitutes good strong contractions before forward perfusion is restarted In aortic valve lesions where there often may be some degree of insufficiency present, it is very important that the left ventricle be beating at the time that forward coronary perfusion is restored Otherwise irreversible left ventricular distension can occur Two fatalities from this cause following potassium citrate asystole are summarized below

An alternative method has been to add enough acetylcholine to the perfusing blood to maintain the arrest even though the retroperfusion continues This procedure is deemed more feasible where a longer period of arrest might be needed such as in coronary artery surgery

Early in our clinical experience with retroperfusion, the coronary sinus was perfused with a separate Sigmamotor Pump calibrated to deliver a predetermined flow of arterial blood to the myocardium This technique was simplified subsequently by removing the pump and securing oxygenated blood directly from the main

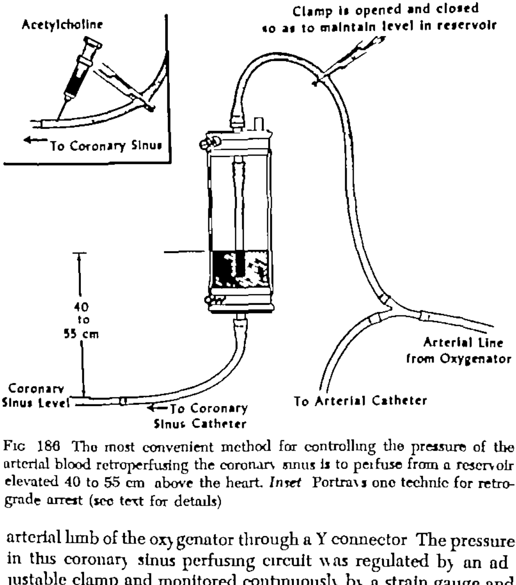


FIG 186 The most convenient method for controlling the pressure of the arterial blood retroperfusing the coronary sinus is to perfuse from a reservoir elevated 40 to 55 cm above the heart. *Inset* Portrays one technic for retrograde arrest (see text for details)

arterial limb of the oxygenator through a Y connector The pressure in this coronary sinus perfusing circuit was regulated by an adjustable clamp and monitored continuously by a strain gauge and Sanborn twin viso recording apparatus Although the two foregoing methods provided a proper coronary sinus flow the technique of perfusing from a reservoir at 50 cm. has been the simplest and therefore the most satisfactory for clinical use (Figure 186)

ing pressure for this retrograde coronary sinus flow is a mean of about 35-40 mm Hg. We have achieved this perfusion pressure by several technics but the simplest method has been to perfuse the coronary sinus from a reservoir of oxygenated blood approximately 50 cm above the heart. The blood volume in the reservoir is maintained by an inflow of arterial blood from the oxygenator (Figure 186). After starting the retroperfusion the ascending aorta is cross clamped and if an aortic valvuloplasty is to be performed, the ascending aorta is incised longitudinally. The diseased valve is then repaired under direct vision. When the valvuloplasty is completed, the aortotomy is reapproximated by application of a suitable vascular clamp and carefully closed with a running silk suture. Any residual air within the aorta is expelled by the retrograde flow as the aortotomy is sutured. As soon as the aortotomy has been closed, the retroperfusion is terminated and the clamp removed from the aorta, restoring forward coronary perfusion.

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In the congenital valvular lesions although the cusps were indeterminate in number the leaflets were in all instances soft and pliable allowing a precise commissurotomy under direct vision In all congenital valvar stenoses we have converted the valve opening into a bicuspid orifice All the valves in the acquired disease group were heavily laden with calcium which in some cases virtually obliterated the cusp-commissure landmarks Three of these had severe stenosis and the fourth had a predominant regurgitation with the valve fixed in a three-quarters open position These valves were examined thoroughly at the time of surgery and if the commissures could be delineated they were incised carefully using either a scalpel or scissors If the commissures were completely obliterated two opposing incisions were made thus forming a bicuspid valve which seemed to function very well (Case 1 Table I) Occasionally calcified spicules acting as struts between the cusp margins and the intima of the aorta within the sinuses of Valsalva were found and removed. In all cases Hegar dilators or the surgeon s fingers were passed through the valve to insure an adequate orifice and to aid in mobilizing the leaflets following the placement of these incisions Pressures were recorded in the left ventricle and aorta before and immediately after valvuloplasty in four of the patients and these are listed in Table I The improvement in the respective pressure gradients after valvuloplasty is apparent from these data One of the best results was achieved in a patient (W M) who had a subvalvular diaphragm A wide incision of this diaphragm completely abolished the 100 mm Hg pressure gradient between the ventricle and aorta

Four of the seven patients with aortic stenosis have shown excellent clinical improvement as a result of their direct vision valvuloplasty and are living and well at this time Likewise the patient with predominant aortic regurgitation has achieved and maintained an excellent clinical improvement following mobilization of her aortic leaflets under direct vision

There were three deaths amongst this group of eight aortic valvuloplasties One patient (J H) had a severely calcified aortic valve and one of the commissure incisions apparently created an intolerable insufficiency which contributed to his death two days after surgery A fifteen year old boy (J D) sustained an unfortu

Clinical Results with Coronary Retroperfusion

The relevant data on the eleven patients undergoing retroperfusion is listed in Table I (pages 472-473)

AORTIC VALVOTOMY

Thoracotomy Incision. The preferred incision for aortic commissurotomy under direct vision utilizing the pump-oxygenator, has been a standard thoracotomy through the bed of the right fourth rib with the patient in a straight lateral position and positioned on the operating table so that the kidney rest lies directly under the incision Elevation of this rest after the chest has been opened gives excellent exposure to the ascending aorta The caval cannulations and access to the coronary sinus for retroperfusion are readily accomplished from this approach The arterial cannula has been inserted either into the right subclavian or common femoral artery

The first patients operated upon by us for aortic stenosis in which the pump oxygenator was used for total cardiopulmonary by-pass, had a bilateral anterior thoracotomy, but the exposure of the aortic valve is not improved over the unilateral (right) thoracotomy, and the likelihood of respiratory complications from the more extensive bilateral incision is certainly greater

In several of the patients with congenital aortic stenosis where there was evidence of such possible associated defects as patent ductus arteriosus, pulmonary stenosis, or left superior vena cava, we have continued utilization of the bilateral thoracotomy to allow management of these associated lesions at the same time

Aortotomy After investigating several types of incisions in the aorta, we believe the most feasible to be a longitudinal hockey stick aortotomy which curves as the annulus is approached so that it ends up almost parallel with the annulus and just above it This incision prevents extensions into the coronary arteries by inadvertent tears, and also the flap-like opening provided improves the visualization of the aortic valve cusps

Results. Eight patients had aortic valve disease Three of these individuals had congenital valvular stenosis, one had a congenital subvalvular stenosis, and in the remaining four patients the aortic valve was the site of acquired disease

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TABLE I

DATA ON ELEVEN PATIENTS HAVING RETROPERFUSION OF THE CORONARY SINUS DURING TOTAL CARDIOPULMONARY BY-PASS

Case & Age (Yrs)	Lesion	Retroperfusion: Technique	Retroperfusion: Duration (Min)	Operative Procedure	Pressures Pre: Aorta / L Ventricle	Pressures Post: Aorta / L Ventricle	Clinical Result
Case 1 39	Acquired Calcific Aortic Stenosis	Separate Retroperfusion Pump (Flow = 125 cc per minute)	14	Created bicuspid valves because of obliterated cusps	—	—	Excellent
Case 2 52	Acquired Calcific Aortic Regurgitation and Stenosis Mitral Stenosis	Separate Retroperfusion Pump (Flow = 125 cc per minute)	13	Aortic Commissurotomy together with mobilization of leaflets by excision of synechia in the sinuses of Valsalva Mitral Valvuloplasty	88/42 104/8	84/46 92/10	Excellent
Case 3 24	Congenital Subvalvular Stenosis	Y-Connector in arterial limb	10	Incised the subvalvular diaphragm	95/65 200/10	90/55 90/15	Excellent
Case 4 38	Acquired Calcific Aortic Stenosis	Perfusion from reservoir at height of 40 cm	2*	Commissurotomy	—	—	Excellent
Case 5 5	Congenital Aortic Stenosis	Perfusion from reservoir at height of 50 cm	2**	Commissurotomy	100/80 145/5	130/85 145/10	Excellent

* 200 mg of acetylcholine injected in retrograde catheter after retroperfusion started, then had 8 minutes of total ischemia with bradycardia of 30

** 60 mg of acetylcholine injected in retrograde catheter after retroperfusion started, then had 10 minutes of total ischemia with bradycardia of 8 beats/minute

TABLE I (*Continued*)

Case 6 28	Acquired Calcific Aortic Stenosis	Separate Retroperfusion Pump (Flow = 125 cc per minute)	14	Commissurotomy	130/120 210/[illegible]	125/0 125/45	Died 2 days postoperatively from aortic insufficiency
Case 7 15	Congenital Aortic Valvular and Subvalvular Stenosis	Y Connector in arterial line	32	Commissurotomy	80/15 175/13	—	Died ... hemorrhage from tears in aorta
Case 8 7 Mos	Congenital Aortic Stenosis	Perfusion from reservoir at height of 50 cm	7	Commissurotomy		—	Died 8 hrs postoperatively. Severe fibroelastosis of left ventricle
Case 9 10	Ruptured Sinus of Valsalva	Separate Retroperfusion Pump (Flow = 80 cc per minute)	10	Closed defect with interrupted sutures	104/6 (aorta)	108/6 (aorta)	Excellent
Case 10 9	Transposition	Y-Connector in arterial line	16	Transplanted base of aorta with cusp and coronaries to cardiac stump of pulmonary artery			Died postop. Unknown cause
Case 11 7 Mos	Aortic Pulmonary Window	Pumped in 10 cc blood/min from bottle of arterial blood	10	Division of communication with lateral closure of defect			Died 10 hrs postop in resp. distress. Severe pul. hypertension preop. A-P window was completely closed

nate event when a transverse aortotomy just above the coronary arteries was utilized During dilatation and excision of the subvalvular component of his stenosis, this circular incision was torn, completely transecting the ascending aorta The aorta was reanastomosed during thirty-two minutes of retroperfusion, during which time the heart continued to beat very well Unfortunately five minutes of cardiac inflow stasis was required after termination of the retroperfusion to complete the repair of leaks in the posterior suture line of the aorta The combination of this anoxia, together with hemorrhage, caused the heart to go into irreversible ventricular fibrillation The third death was in a seriously ill infant (P K) who had a congenitally stenotic valve opened widely under direct vision The operative procedure and immediate postoperative interval were uncomplicated There was no postoperative aortic insufficiency She died suddenly eight hours after surgery and postmortem revealed severe endocardial fibroelastosis of the left ventricle which apparently led to her demise

Surgical Results in Other Lesions Using Retroperfusion

Retroperfusion of the coronary sinus has been utilized for the repair of three other types of cardiac lesions [3,10] A girl (Case 9, Table I) had a ruptured aneurysm of a sinus of Valsalva into the right ventricle Utilizing retroperfusion, the ascending aorta was cross-clamped to prevent a deluge of back bleeding through the defect A completely dry field then permitted an easy closure of the ruptured sinus with interrupted sutures placed via a right ventricular cardiotomy The patient remains cured at this time A two year old boy (Case 10, Table I) had complete transposition of the great vessels, and during 16 minutes of retroperfusion the ascending aorta was transplanted, complete with aortic cusps and coronary arteries, and anastomosed to the proximal segment of the transected pulmonary artery The distal portion of the pulmonary artery in turn was connected to a newly created orifice in the right ventricle by a homograft The duration of the total cardiopulmonary by-pass was 1 hour and 17 minutes The heart beat took over in an excellent fashion and the repairs appeared to function well However, death occurred several hours later, possibly as

a result of the valveless pulmonary artery and pulmonary hyper tension The third patient in this series was a two month-old girl (Case 11 Table I) with an aortic pulmonary septal defect in the usual location just distal to the aortic leaflets Using retroperfusion this fistula was divided under direct vision and the lateral defects in the aorta and pulmonary artery repaired The patient had severe respiratory distress beginning on the third postoperative day and died ten days after surgery Postmortem examination showed complete correction of the septal defect together with a diffuse bronchiolitis obliterans and widespread severe intimal pul monary arteriolar proliferation No doubt the child s severe pul monary hypertension and occlusive arteriolar lesions were a major contribution to her death from the superimposed inflam matory lesions in her lungs In each of these eleven patients the retroperfusion maintained the heart well and free of the development of arrhythmias None of the hearts developed ventricular fibrillation during or immediately after their interval of retroper fusion except Case 7 (Table I) in which there were obvious com plicating factors

OTHER TECHNICS FOR EXPOSURE OF AORTIC VALVE AREA

At the present time there are several technics available to the cardiac surgeon which permit direct vision surgery in the area of the aortic valve and ascending aorta

Hypothermia Hypothermia which has been used by Lewis[5] and Swan[6] appears to have two serious disadvantages namely a restriction of operative time in this area and an increased irritabil ity of the myocardium

Potassium Citrate Asystole In this clinic, retroperfusion of the coronary sinus in combination with a pump-oxygenator was first used on a patient in January 1956 At that time no other oxygena tor technique was available for exposure of the aortic valve Retro- perfusion has worked very well but does entail the additional sometimes difficult cannulation and purse string suturing of the catheter into the coronary sinus ostium Thus when the cardio- plegic drugs became available and had proven satisfactory for other types of intracardiac defects[7, 8] such as ventricular defects

nate event when a transverse aortotomy just above the coronary arteries was utilized. During dilatation and excision of the subvalvular component of his stenosis, this circular incision was torn, completely transecting the ascending aorta. The aorta was re-anastomosed during thirty-two minutes of retroperfusion, during which time the heart continued to beat very well. Unfortunately five minutes of cardiac inflow stasis was required after termination of the retroperfusion to complete the repair of leaks in the posterior suture line of the aorta. The combination of this anoxia, together with hemorrhage, caused the heart to go into irreversible ventricular fibrillation. The third death was in a seriously ill infant (P.K.) who had a congenitally stenotic valve opened widely under direct vision. The operative procedure and immediate postoperative interval were uncomplicated. There was no postoperative aortic insufficiency. She died suddenly eight hours after surgery and postmortem revealed severe endocardial fibroelastosis of the left ventricle which apparently led to her demise.

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one normal commissure and two fused ones resulting in a valve orifice of 12 to 14 mm in diameter The exposure was excellent The two fused cusps were carefully incised to the aortic annulus and the leaflets mobilized resulting in what appeared to be an excellent valvuloplasty Following this the aortotomy was closed and the aortic cross clamp removed after an arrest period totaling eleven minutes

The left ventricle remained in complete arrest and was absolutely resistant to all attempts to restart it Sequentially massage adrenalin calcium and electrical stimulation were utilized without avail. The left ventricle continued to distend unless emptied manually After 90 minutes of perfusion during which these efforts continued the patient was pronounced dead.

Autopsy disclosed an excellent commissurotomy Massive left ventricular hypertrophy was present An incidental finding of interest was a functioning pheochromocytoma of the right adrenal gland

Case 2: This eight year-old boy was known to have a heart murmur since 14 months of age Cardiac catheterization and exploratory thoracotomy for a patent ductus arteriosus was carried out elsewhere at the age of five years No ductus was found The pericardium was opened and a very pronounced thrill was found in the right ventricle The aorta was enlarged, actively pulsating, and together with the continuous thrill resulted in the diagnosis of ruptured aneurysm of the sinus of Valsalva The operative procedure was then terminated. Subsequent recatheterization and angiocardiography were interpreted as confirmatory of this diagnosis

Physical findings at the time of admission were a blood pressure of 108/0 a palpable thrill over the precordium and a loud continuous murmur heard over the sternum and transmitted to the right and left and to the back.

On April 29 1957 corrective surgery was carried out Upon opening the pericardium a very substantial thrill was present in the right ventricle as previously described This thrill appeared to originate from the aorta in the region of origin of the right coronary artery This fact together with some aneurysmal dilatation in this region led to the diagnosis of a ruptured aneurysm of the sinus of Valsalva The aorta was much enlarged, contrasted with the usual case of ventricular defect, and this too seemed to be in favor of a ruptured sinus of Valsalva aneurysm

and tetralogy of Fallot, we felt that cardioplegia could be the answer to a simplified method for temporary aortic valve exposure. Our initial experience with cardioplegia for aortic valve disease was with potassium citrate. Both patients died on the operating table due to an inability to restart their hearts after only very brief periods of asystole. A brief summary of these two chastening experiences with complete cardiac arrest in patients with advanced aortic valvular disease are summarized below.

Case 1: The recent symptoms in this 38-year-old man which led to his referral for corrective surgery, were inability to work because of dyspnea and decreased physical strength associated with episodes of syncope upon mild exertion. A systolic murmur over the aortic area was first detected in 1946 while he was still in the army. In 1952 he was hospitalized for this disability for the first time. In 1954, he developed subacute bacterial endocarditis which was successfully treated during a prolonged interval of hospitalization.

Physical examination disclosed a palpable thrill in the aortic area with a loud blowing systolic murmur with its maximal intensity over the aortic valvular area, radiating up into the neck and in all directions. There was also a blowing diastolic murmur audible in the aortic area and transmitted down along the left sternal border of the sternum. The blood pressure was between 140/60 to 160/80 at various examinations.

Roentgenography showed marked cardiomegaly due to left ventricular enlargement, and calcification of the aortic valve area was readily apparent. The electrocardiogram was abnormal due to marked left ventricular hypertrophy and strain.

The to-and-fro murmurs and other findings confirmed the diagnosis of calcific aortic stenosis and insufficiency.

Operation was undertaken March 27, 1957, entering the chest through the bed of the right fourth rib with the patient in a lateral position. The ascending aorta was huge in size and a pronounced systolic thrill was present in it. There was also a marked diastolic thrill in the left ventricle.

The patient was linked to the pump-oxygenator in the usual fashion, by-passing the heart and lungs. The aorta was cross-clamped proximal to the innominate artery, and 120 cc. of 2½% potassium citrate injected into the first portion of the aorta produced asystole. The ascending aorta was then opened, disclosing

In such heart it is understandable why potassium citrate which gives a profound degree of relaxation of the cardiac musculature when perfused into the coronary circulation is so dangerous The problem appears to be primarily although perhaps not entirely a mechanical one viz. inability to wash out the potassium citrate even though as in these two cases the perfusing head of pressure be raised to levels above normal

After these two tragic experiences with potassium citrate we have abandoned its use for aortic valve surgery These two patients both had very severe aortic valvular disease with marked left ventricular myocardial hypertrophy One patient had only four minutes of arrest and the other eleven minutes In each when the aortic clamp was removed restoring coronary perfusion to the paralyzed myocardium the flaccid left ventricle distended severely augmented by the slight degree of aortic insufficiency which is present in many if not most of these cases The extreme distension of an ischemic flaccid heart in combination with a poorly perfused hypertrophied myocardium led to irreversible fibrillation in both cases Moreover effective massage is usually difficult because of the massive concentric hypertrophy of these hearts After these two poignant experiences with complete cardiac arrest in cases with advanced left ventricular disease it was realized that ideally the heart should be beating during the valvuloplasty or before systemic blood pressure was restored to the aortic valve The contracting left ventricle could then eject any blood that might flow back through slightly regurgitant valves when the clamp on the ascending aorta was removed

Case 2 illustrates another lesson worthy of emphasis namely the folly of arresting the heart before opening it to inspect the nature of the pathology To date we have utilized induced cardioplegia in over one hundred patients and this patient is the only one in the series in which we have arrested the heart before ventriculotomy In this particular patient we were misled by the fact that the external pathology appeared so typical of ruptured aneurysm of a sinus of Valsalva together with the fact that potassium citrate asystole had worked well in two patients[10] with this pathology

Total Cardiac Ischemia Since aortic commissurotomy in some

After insertion of caval and arterial catheters, by-passing the heart in the usual fashion, the ascending aorta was cross-clamped just below the innominate artery, and 50 cc of 2½% solution of potassium citrate diluted in blood was injected into the proximal aorta. This resulted in a prompt asystole and a right ventriculotomy was carried out disclosing, instead of the anticipated ruptured aneurysm, a moderately sized (1.5 cm.) congenital membranous defect in the ventricular septum with complete incompetence of the aortic valve. Sutures were placed across the ventricular defect and several were tied. Before completing tying the remainder, the clamp was removed from the aorta in order to re-establish the cardiac beat after a period of asystole of only four minutes. However, throughout the remainder of the perfusion, lasting two hours, no left ventricular beat could be re-established.

Whenever an attempt was made to try to close the defect or close the right ventricle, the left ventricle would enlarge tremendously. To control this complication, a tourniquet was even passed around the aortic annulus and beneath the coronary arteries to allow coronary perfusion and to prevent left ventricular distention. This was without effect upon the completely paralyzed left ventricle. Eventually the ascending aorta was opened and an attempt was made to repair the aortic insufficiency by direct suture of the leaflets converting them into a bicuspid orifice. This was successful in controlling the regurgitation, but we were unable to restore a heart beat.

Pathologic Physiology. In advanced aortic valvular disease the left ventricular hypertrophy is massive, and doubtless exceeds the available coronary supply, even though the latter may be entirely free of arteriosclerotic disease. This relative coronary insufficiency was the basis for the sudden deaths due to ventricular fibrillation characteristic of these patients. Moreover, it is not uncommon for the myocardium in hearts with advanced left ventricular hypertrophy to exhibit areas of ischemic necrosis. This latter finding is particularly liable to be present in the inner layers of the myocardium where the high left ventricular pressures constitutes an added obstacle to the coronary circulation. If in addition there is superimposed some coronary artery obstructive disease as often happens in older patients with acquired lesions, it is obvious that the blood supply to these hearts can often be submarginal.

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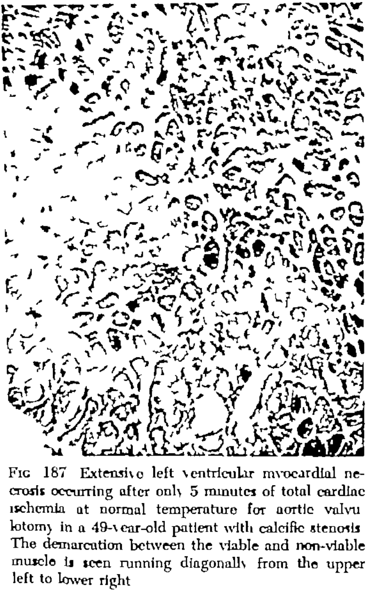


FIG 187 Extensive left ventricular myocardial necrosis occurring after only 5 minutes of total cardiac ischemia at normal temperature for aortic valvulotomy in a 49-year-old patient with calcific stenosis The demarcation between the viable and non-viable muscle is seen running diagonally from the upper left to lower right

very responsive to external stimuli such as massage and thus the beat may be more quickly restored This obviates the complication of ventricular distension encountered with the profound relaxation of potassium citrate arrest. The technique of using acetylcholine is not without some danger however for the slowly beating ischemic heart may be utilizing more energy than the completely

patients at least, can be carried out under direct vision quite adequately within only 2 to 4 minutes of working time, the possibility occurred to us early in this work that one might simply ignore the myocardial oxygen requirements of the by-passed heart for this brief period

The theoretical attractiveness of this approach has been further enhanced by the many recent experimental studies and a number of human observations, indicating that the heart is surprisingly tolerant to anoxia In a recent patient, documented elsewhere,[9] we observed the heart to recover sinus rhythm spontaneously after thirty-five minutes of total ischemia without cardioplegia Moreover, convalescence was uncomplicated by any arrhythmias However, this patient, as do the experimental animals on which much of this information is based, had a good myocardial reserve to start with This is obviously not true of patients with aortic valve disease Thus, we have not been particularly attracted to this approach, as previously stated,[1] in which elective anoxia is used However, we did try this method in a forty-nine-year-old patient with acquired calcific aortic stenosis Commissurotomy was carried out, utilizing total cardiopulmonary by-pass during only five minutes of complete myocardial ischemia at normal temperature The heart continued to beat during this time, for no cardioplegic drug was used Despite the very short period of ischemia and an excellent commissurotomy, as established by pressure determinations* at surgery and confirmed later at autopsy, this patient died suddenly thirty-six hours after surgery and exhibited at postmortem extensive necrosis of the inner one-third of the ventricular myocardium (Figure 187)

Use of Acetylcholine Asystole We have had experience with six patients with aortic valve disease utilizing total cardiopulmonary by-pass at normal temperature, together with acetylcholine induced asystole (Table II)

In general, this experience has been quite satisfactory and certainly if cardioplegia is to be used in these hearts, acetylcholine appears to be safer than potassium citrate

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	Left Ventricle	Aorta (mm Hg)
* Pre-correction	225/30	100/75
Post-correction	100/22	75/40

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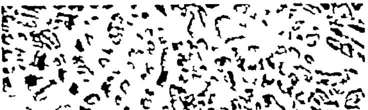


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TABLE II

AORTIC VALVE SURGERY UTILIZING TOTAL CARDIOPULMONARY BY-PASS WITH ACETYLCHOLINE* ASYSTOLE

Case & Age (Yrs)	Lesion	Minutes Duration of Total Bypass	Minutes Duration of Arrest	Arrhythmias	Result
Case 1 5	Congenital Valvular	12	8	Ventricular Fibrillation**	Excellent
Case 2 22	Congenital Valvular	20	7	None	Excellent
Case 3 11	Congenital Subvalvular	12½	7	Ventricular Fibrillation**	Excellent
Case 4 6 Mos	Congenital Valvular	18	5	Cardiac Arrest 6 hrs postop Good Recovery	Died 48 hrs postop No clear cut cause of death Debilitated preoperatively
Case 5 7	Congenital Valvular	17	6	Ventricular Fibrillation**	Excellent
Case 6 49	Calcific Aortic Stenosis	62	53	Ventricular Fibrillation**	Died 2½ days postop of left ventricular failure Debilitated preoperatively

* 10 mg/kg body weight
** Developed shortly after restoration of coronary arterial flow Easily defibrillated with electric shock and pump-oxygenator support

stilled heart The much greater incidence of ventricular fibrillation in these hearts (Table II) in comparison to those with retrograde coronary perfusion is undoubtedly significant in that regard For these reasons the period of ischemia utilizing acetylcholine should be brief It does appear from the experience in this small clinical series that acetylcholine cardioplegia can be used safely for aortic stenosis if this period of ischemia is no longer than ten to fifteen minutes, the myocardium is not greatly hypertrophied, and the cardiac reserve reasonably good

However, Case 6 (Table II) illustrates the fact that it may not be possible to be certain *a priori* of the duration of any intracardiac procedure In this man the initial commissurotomy resulted in an obvious aortic insufficiency In the subsequent interval, it was possible to obtain an excellent reparative result upon the valve, preserving an adequate orifice and correcting the insufficiency by suturing the leaflets to form a bicuspid valve, but the

cardiac ischemia was severe It is possible that retrograde perfusion during this interval might have made the difference between success and failure in this case

CURRENT PROCEDURE FOR AORTIC VALVE LESIONS

At the present time we are using total cardiopulmonary by pass together with acetylcholine asystole for the patients with congenital aortic stenosis

In most patients with acquired stenosis where the valve is severely diseased the ventricular myocardium is greatly hypertrophied and a longer period of time is contemplated for the valvuloplasty retrograde perfusion of the coronary sinus undoubtedly is the safest procedure that can be recommended at this time

CONCLUSIONS

1 Retrograde perfusion of the coronary sinus in combination with a pump-oxygenator has been used in eleven patients for a variety of cardiac lesions involving the left heart

2. Five of the eight patients with aortic valvular disease survived the operative procedure and attained excellent clinical improvement following direct vision valvuloplasty

3 Three additional patients have undergone reparative procedures using retroperfusion An individual with a repaired ruptured aneurysm of a sinus of Valsalva is living and well at this time The second patient an infant, had an aortic pulmonary communication divided, but died ten days postoperatively of respiratory complications The last infant had complete transposition of the great vessels and died following corrective surgery involving transplantation of the ascending aorta aortic valve and coronary arteries

4 In all of these eleven operations the retroperfusion of the coronary sinus appeared to protect the myocardium eminently well against anoxia There were no instances of cardiac arrhythmia even though a number of the patients had far advanced left ventricular disease

5 Acetylcholine has also been used in combination with the retroperfusion in two patients It is injected into the retrograde catheter providing a dry still field while the aortic valvuloplasty

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AORTIC VALVE SURGERY UTILIZING TOTAL CARDIOPULMONARY BY-PASS WITH ACETYLCHOLINE* ASYSTOLE

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is being performed Both patients had an excellent clinical result

6 Total cardiac ischemia of brief duration resulted in extensive myocardial necrosis in one patient with acquired aortic stenosis, and this approach is not recommended for aortic valve surgery

7 Evidence is advanced to support the belief that total cardiac ischemia, even with the additional protection offered by potassium citrate asystole, is also a dangerous practice in hearts afflicted with the advanced states of aortic valve disease It was not possible to restore a left ventricular beat in either of the only two patients in whom it was utilized

8 Acetylcholine asystole with total cardiopulmonary by-pass has been utilized in 6 patients with aortic valvular disease, and has proved of value when the arrest interval was brief However, a significantly greater incidence of arrhythmias occurred than when retroperfusion was utilized

9 Current practice has been to use the acetylcholine arrest in patients with congenital lesions where the operative repairs require less time and the myocardia generally have a greater reserve Retrograde perfusion of the coronary sinus, together with retrograde acetylcholine cardioplegia when needed to facilitate exposure, is the recommended procedure for patients with advanced degrees of acquired aortic valvular pathology

10 Although acetylcholine cardioplegia (without retroperfusion) appears to be the simpler technique for aortic valve exposure, retrograde perfusion is undoubtedly the safer method when there is marked myocardial hypertrophy and a longer period is contemplated for the valvuloplasty

11 The concept of correcting aortic regurgitation by converting the valve leaflets (by suture) to a bicuspid orifice is suggested

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DISCUSSIONS

DR WILLIAM E ADAMS, Chicago Dr Gerbode and gentlemen It is certainly a privilege to be here for this meeting and to hear this wealth of material which has been presented in the last three days on this very important problem

I am sure you all feel that the work which has been presented was varied in character, sometimes there has been some disagreement, but in general one might say that people have come together from many different approaches to this problem

I have been asked to say a few words about "elective asystole" in connection with extracorporeal circulations I am sure there are a number of you who could do a much better job of this assignment than I, but I will try to present our point of view in the light of our work and also of the presentations which have been made at this conference Of course, this problem needs to be considered as a whole, that is, the effect on the brain as well as the heart and other organs must be taken into consideration I believe, in earlier work, damage to the brain was given more emphasis than perhaps was warranted At the present time it would appear that damage to the heart is likely to occur more quickly and severely than to the brain For reasons such as you have heard, there have been various means and methods used for protecting the heart Contrary to some statements to be found in the literature, in 1938 we found that on occlusion of the inflow tract to the heart of a normothermic anaesthetized dog, the heart would continue for at least 5 minutes and seemingly recover without irreparable damage on release of the occlusion or obstruction of the venae cavae and azygos veins We had some dogs go as long as 9 minutes followed by recovery and no evidence of brain damage

There have been some statements made that the normal dog with a normally beating heart with the inflow tract occluded does not use more oxygen than one under arrest In our experience earlier and more recently with Dr Moulder, we found that under normothermic conditions a heart that continues to beat after the inflow tract is obstructed will become darkened and actually cyanotic This will also occur in hypothermic conditions but it is more delayed, whereas the arrested heart in our experience will remain pink Blood coming from the heart muscle will be of good color when it starts to beat again The amount of oxygen extracted from the coronary circulation of a dog with an arrested heart at 25°C was found to be 3 to 4 volumes per cent from a perfusion of 1-5 ml blood for kg body wt per minute Therefore, al-

though I was interested in the excellent work presented by Dr Bing I can t quite correlate his findings with the remarks of Dr Sarnoff as well as our own observations Perhaps the experimental conditions were not identical If therefore anoxia or hypoxia is a very important factor in causing damage of the heart muscle elective arrest should be an effective method for its prevention

I would like to make one other remark and that is this—from the comments and presentations made at this meeting it would appear that there might be a definite trend toward a combination of methods or procedures to attain the best operative results Namely a combination of extracorporeal circulation hypothermia in the range of 30 or 32°C degrees and controlled cardiac arrest

DR. RUSSELL M NELSON Salt Lake City Thank you very much Dr Gerbode and Dr Moore for the invitation to discuss the present status of our work in progress on cardioplegic agents

To date in this series of experiments my associates James Mason Gary Maxwell Joseph Nelson John Peters Richard Hardy and I have subjected forty five dogs to cardiopulmonary by pass employing Sigmamotor pumps and a modification of our bubble oxygenator reported previously Flow rates have been at 50 ml /kg /min and the temperature has been carefully controlled After screening the effects of many agents in frog heart perfusions drugs were tried in dogs to assess any cardioplegic effect (Table I)

With acetylcholine as a familiar standard for comparison these other drugs with cholinergic properties were tried. Carbachol produced

TABLE I

CHOLINERGIC DRUGS (Nelson)

Agent	*Dose*	*No. of Trials*	*Initial Effect*	*Recovery*	*Remarks*
Acetylcholine	10 mg /kg in 20 cc blood	8	Asystole	N.S.R.	Relaxed flabby heart which is easily excitable Excellent recovery
Methacholine	8 mg in 20 cc. blood	1	Brief asystole (less than 1 min)	N S R.	
Carbachol	0 8 mg. in 20 cc blood	1	Fibrillation	None	
Carbachol	1 mg in 20 cc blood	2	Asystole	N.S.R.	Like Acetylcholine Atropine necessary for reversal.
Neostigmine	[illegible] mg in 20 cc blood	1	Slight bradycardia	N.S.R	
Tensilon Chloride (Edrophonium)	100 mg in 20 cc blood	1	No immediate effect	Ventricular tachycardia, fibrillation	Tachycardia started 8 min after clamp removed from aorta.

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TABLE IV

ANTIHISTAMINICS AND LOCAL ANESTHETICS (Nelson)

Agent	Dose	No. of Trials	Initial Effect	Recovery	Remarks
Procaine HCl	0.1 gm. in 20 cc. blood	1	Bradycardia ECG alterations	N.S.R.	
Procaine HCl	0.2 gm. + 10 cc. blood	1	Bradycardia ECG alterations	N.S.R.	20 min. needed for complete ECG recovery
Procaine HCl	0.5 gm. in 20 cc. blood	2	Asystole	V. Fibrillation	Flabby non-excitable heart
Benadryl	20 mg. in 20 cc. blood	1	Bradycardia	N.S.R.	
Benadryl	200 mg. in 20 cc. blood	1	Asystole	N.S.R.	Prolonged recovery (60 min.)
Benadryl	400 mg. in 20 cc. saline	1	Asystole	N.S.R.	Prolonged recovery (60 min.)
Chlor-trimeton	50 mg. in 20 cc. saline	1 (?)	Weak, slow contraction	N.S.R.	Prolonged recovery
Chlorpromazine	100 mg. in 20 cc. saline	1	Progressive deterioration of contraction and ECG	None	Cyanotic patches in heart

able to those employed for potassium citrate arrest. These hearts all fibrillated after the coronary perfusion was resumed.

Magnesium sulfate caused ventricular fibrillation.

Curare and succinyl choline produced no discernible effect on cardiac activity, but quinidine poisoned the heart in this instance just as it has done in other series of experiments (Table III).

Procaine, in adequate dosage, produced asystole, but recovery was prolonged and variable (Table IV).

Of great interest was the observation that Benadryl produced a profound state of cardioplegia. The heart is non-excitable and is very stable through the period of perfusion. I would caution against its

TABLE V

MISCELLANEOUS DRUGS (Nelson)

Agent	Dose	No. of Trials	Initial Effect	Recovery
2 (omethylphenol) cyclohexanol	8 cc. of saturated saline solution	1	No change	N.S.R.
	0.2 cc. in 20 cc. blood	1	Asystole	None
Hypaque	20 cc. of a 50% solution	2	V. Fibrillation	None
Versene	1 gm. in 20 cc. saline	2	Asystole	V. Fibrillation

TABLE II

IONS (Nelson)

Agent	*Dose*	*No of Trials*	*Initial Effect*	*Recovery*	*Remarks*
Potassium Citrate	1 5 m Eq in 20 cc blood	5	Asystole	N S R	Heart is relaxed and flabby with a pink color Recovery is rapid Blood temp 96–99°
Potassium Citrate	1 5 m Eq in 20 cc blood	1	Asystole	V Fibrillation	Blood temp 92°
Potassium Chloride	6 m Eq in 20 cc blood	1	Few extrasystoles by ECG	N S R	
Potassium Chloride	6 m Eq in 20 cc blood	1	Asystole	N S R	Asystole not produced until aortic clamp removed
Potassium Chloride	12 m Eq in 40 cc blood	1	Asystole	V Fibrillation	
Lithium Citrate	2 m Eq in 20 cc blood	1	Asystole	V Fibrillation	Flabby heart, like potassium Citrate
Sodium Citrate	1 4 m Eq in 20 cc blood	3	Asystole	V Fibrillation	Asystole as with Potassium Citrate
Sodium Chloride	30 cc 0 9%	1	No Change		No Change noted
Sodium Lactate	6 m Eq in 20 cc blood	1	Slight bradycardia	N S R	Essentially no effect
Magnesium Sulfate	4 m Eq in 20 cc blood	1	V Fibrillation	None	Pink heart with slow fibrillation
Magnesium Sulfate	10 m Eq in 20 cc blood	1	V Fibrillation	None	

a quiet, but excitable heart, as did acetylcholine, but atropine was necessary for reversal to a normal sinus rhythm (Table II)

With potassium citrate arrest by the Melrose technic, satisfactory recovery of the normal sinus rhythm regularly occurred except in one instance when the temperature was below normal This has been noted in other series as well

Asystole could be produced with potassium as the chloride salt only in higher doses, and then was seen only after the aortic clamp was removed

Citrates of lithium and sodium arrested the heart in doses compar-

TABLE III

MUSCLE RELAXANTS (Nelson)

Agent	*Dose*	*No of Trials*	*Initial Effect*	*Recovery*
Curare	6 mg in 20 cc blood	1	No change	N S R
Succinyl Choline	250 mg in 20 cc blood	1	No change	N S R
Quinidine	600 mg in 20 cc blood	1	Fibrillation	None

TABLE IV

Antihistaminics and Local Anesthetics (Nelson)

Agent	*Dose*	*No. of Trials*	*Initial Effect*	*Recovery*	*Remarks*
Procaine HCl	0.1 gm. in 50 cc. blood	1	Bradycardia ECG alteration	N.S.R.	
Procaine HCl	0.2 gm. +10 cc. blood	1	Bradycardia ECG alteration	N.S.R.	30 min. needed for complete ECG recovery
Procaine HCl	0.5 gm. in 20 cc. blood	3	Asystole	V. Fibrillation	Flabby non-excitable heart
Benadryl	20 mg. in 20 cc. blood	1	Bradycardia	N.S.R.	
Benadryl	200 mg. in 20 cc. blood	1	Asystole	N.S.R.	Prolonged recovery (60 min.)
Benadryl	400 mg. in 50 cc. saline	1	Asystole	N.S.R.	Prolonged recovery ([illegible] min.)
Chlor-trimeton	30 mg. 20 cc. saline	1 (4)	Weak, slow contraction	N.S.R.	Prolonged recovery
Chlorpromazine	100 mg. in 20 cc. saline	1	Progressive deterioration of contraction and ECG	None	Cyanotic patches in heart

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TABLE V

Miscellaneous Drugs (Nelson)

Agent	*Dose*	*No. of Trials*	*Initial Effect*	*Recovery*
2 (omethylphenol) Cyclohexanol	8 cc. of saturated saline solution	1	No change	N.S.R.
	0.2 cc. in 20 cc. blood	1	Asystole	None
Hypaque	20 cc. of a 50% solution	2	V. Fibrillation	None
Versene	1 gm. in 20 cc. saline	2	Asystole	V. Fibrillation

use, however, because of an apparent antiheparin effect, and because forty-five to sixty minutes of perfusion on the by-pass are necessary before the recovery is sufficient for independent cardiac adequacy

Of interest here is that hypaque, a contrast medium used by some for coronary arteriography, produced ventricular fibrillation in the two dogs in which it was used Versine, a calcium chelating agent, stopped the heart in two trials, and caused a most fascinating phenomenon in the recovery period characterized by a quiet right ventricle and a beating left ventricle, followed by fibrillation (Table V)

While these results are preliminary in character and the numbers of experiments too small to be significant as yet, certain working postulates may be cautiously advanced

1 The "potassium arrest" produced by the doses of potassium citrate generally employed, is probably, in fact, a "citrate arrest" with potassium exerting a salutory effect in recovery to a normal sinus rhythm

2 Asystole, as produced by the citrates of potassium, lithium and sodium, and the chelating agent, versine, is probably mediated through their binding effect on the calcium ion

DR HENRY T NICHOLS, Philadelphia Our experience with potassium citrate arrest consists of 39 cases and the majority have been patients with either aortic stenosis, aortic insufficiency, or a combination of the two We failed to get the heart restored to a normal beat in only one of these cases However, several have gone through episodes of ventricular fibrillation They have responded to a continuation of the by-pass, massage and electrical defibrillation In many of the cases with a normal beat there was a delay of several minutes before the contractions were effective enough to produce a satisfactory blood pressure In patients where aortic insufficiency has either been created or has not been corrected, we have found it very advantageous to institute cardiac massage to prevent a distended left ventricle In patients with aortic stenosis only, the mortality has been 17 per cent In those with aortic insufficiency, the mortality rate has been 44 per cent.

DR WILLIAM SCOTT, JR , Nashville, Tennesse Dr Gerbode and gentlemen As the last designated and unfortunately the least able discussant in this entire session, I should be in a position to wax philosophical and to synthesize the sense of the conference into a well defined nugget of pure gold This obviously I can't do, but it does seem evident that the trend of the discussion has been to indicate that the more successful application of techniques and apparatus to maintain

extracorporeal circulation will be in the direction of achieving Dr Cannon's concepts of homeostasis in every possible modality and not by deluding ourselves that since the body can tolerate incredible deficits these are acceptable or desirable simply because we can "get away" with them

I have especially enjoyed the superb presentations today on myocardial metabolism in both the beating and non beating heart I suppose to these it should be added, the heart in its beaten states It is obvious that when oxygenation of tissue is inadequate an oxygen debt is incurred This debt is certainly much less in the adequately oxygenated myocardium when no work is being done as in induced arrest but it is there just the same as Dr Bentall and others have indicated It seems reasonable that the oxygen debt must increase with time.

Our group has just started a study of metabolic and functional changes in the heart during and after induced arrest with the hope of working out a plan for reducing the risks of arrest and prolonging the safe period. This would seem especially desirable in the repair of some of the more complicated lesions particularly those on the left side of the heart, such as mitral insufficiency with which we have had some success recently in a small number of patients Our idea has been first to induce arrest and then to use continuous perfusion of the base of the aorta proximal to an occluding clamp and through this perfusion of the coronary arterial circulation with oxygenated blood containing a concentration of the arresting agent. Preliminary experiments in the dog have shown that, after inducing potassium citrate arrest asystole can be maintained for periods of at least an hour and one-half with recovery when oxygenated blood is perfused through the coronary arteries at rates of 15 to 20 ml./min. with no cardioplegic agent. We believe this is a lead worth pursuing

I am sure I speak for all in this audience in telling Doctors Moore Allen, Morrow Swan Gerbode and other members of the Surgery Study section of the USPHS of the fine job they have done in putting this conference together and of the pleasure it has been for us to attend it

DR FREDERICK S CROSS Cleveland I think it is important in each of the various runs with perfusions on the experimental animal to run a series on controls in which the traumatized heart is not arrested and not perfused. Secondly the period of arrest in the test animals should be in the vicinity of forty to forty five minutes Thirdly I think there is tremendous advantage in venting the proximal aorta

Interestingly enough, in our control dogs in which occlusion for

forty minutes was employed and the data were evaluated on the basis of the amount of fibrillation and the length of time required for pump support, and the ability of the heart to take over after it was off the pump, all fibrillated, but were finally defibrillated and took over on their own There was one possible exception However, the incidence of fibrillation was high and it was difficult to defibrillate them The pump-support time was as long as forty-five minutes The heart did not take over well and was slow to revert to a normal pattern

In an attempt to improve our results, we have perfused the proximal aorta with about 200 cc of oxygenated blood at 0 degrees Centigrade We then rewarmed the heart to 20 degrees and the temperature rose to about 29 degrees The results were better in this group in that the heart was easier to defibrillate and the heart took over more quickly We then stopped the heart with potassium citrate and perfused the coronaries with cooled blood at 0 degrees, the combined temperature rising to about 18 degrees In these animals there was a very low incidence of fibrillation, although we used the defibrillator occasionally, and the period required to revert the heart to a normal pattern was shortened

In an attempt to understand the reason for this, we did some experiments on the cardiac metabolites If you will look at the last column on the slide (slide not available) there is a progressive oxygen utilization We tried to differentiate the non-working potassium arrested heart and the cold, non-working heart because we had some difficulty with the potassium-arrest heart Oxygen consumption was reduced somewhat more in the potassium arrested heart than in the heart that has been cooled In nineteen experiments you can see it is 1 9 per cc per minute We did not feel that it was necessarily much better in the potassium plus the cold heart We feel that if there is a problem of mechanical difficulty in the arrested cold heart, the washing out the potassium and at the same time maintaining the arrest may be of benefit when the heart takes over its function as potassium does not have to be washed out later and the heart takes over more quickly

DR JOHN W KIRKLIN, Rochester, Minn Perhaps in any surgical endeavor there is wisdom in an attempt to define the need for further investigation I would like to talk about the need for this in induced cardiac asystole, or whatever one wants to call this state We are not the originators of cardiac arrest We have simply followed the technics of Drs Lam and Melrose, Effler and Groves Our technics have been identical with those of Drs Melrose, Groves, Effler and their asso-

ciates I think in this day of the regular use of induced asystole, we should never forget what has been pointed out to us by these people concerning the great value of this tool

Our experience at the Mayo Clinic has paralleled that of the group at the Cleveland Clinic We agree with everything said about asystole as described by Melrose but we do not feel in dire need of improvement in the clinical aspects of its use for operations within the ventricle That is not to say there will not be a better way of doing it However it has been our experience that induced cardiac arrest with potassium does not predispose to heart block In our hands there has been no difficulty in starting the heart again as long as the total body perfusion is good at the time the clamp is released. We feel that one has safe operating conditions for thirty minutes and probably a reasonably safe one for 40 minutes I merely then wish to re-emphasize everything which has been presented about the usefulness and advantages of induced cardiac asystole

DR DENTON A COOLEY Houston Our experience at Baylor with cardiopulmonary by pass as of two weeks ago included 248 cases Figure 188 I would like to call your attention to specific types of cases since they are particularly important in the discussion of induced cardiac arrest. The cases I will mention are aneurysm of the ascending aorta, aortic stenosis and ventricular septal defect.

CARDIOVASCULAR LESIONS IN 248 CASES OF CARDIOPULMONARY BY PASS

	No
Ventricular Septal Defect	103
Atrial Septal Defect	46
Tetralogy of Fallot	17
Aneurysm Ascending Aorta	12
Atrio-Ventricularis Communis	12
Aortic or Subaortic Stenosis	17
Pulmonic Stenosis	10
Transposition of Great Vessels	4
Common Ventricle	3
Aortico-Pulmonary Septal Defect	3
Total Anomalous Pulmonary Venous Drainage	4
Miscellaneous	17
Total	248

FIGURE 188 (Cooley)

One may employ the pump oxygenator for resection and graft replacement of the ascending aorta In the patient shown in Figure 189, a fifty-year-old man, the proximal aortic clamp was applied for thirty-one minutes with probable occlusion of the coronary ostia Cardiac arrest from anoxia resulted after about twelve minutes When flow was

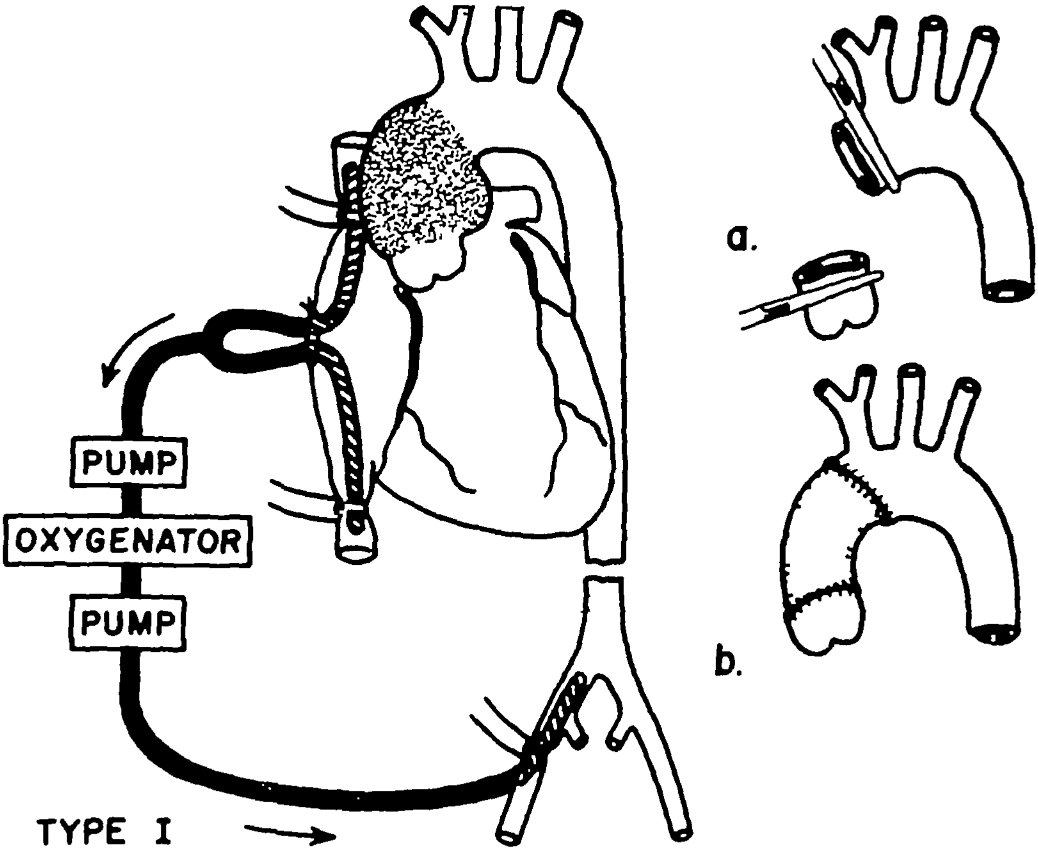


FIGURE 189 (Cooley)

re-established in the coronary arteries, ventricular fibrillation occurred which responded to electrical defibrillation This patient has fully recovered and more than one year after operation is active and has no residual myocardial damage This type of procedure, however, does not seem to be safe in older patients, particularly those in the sixty- to sixty-five-year age group Furthermore, at present we do not believe that induced potassium arrest should be used in the older patient with an arteriosclerotic heart Results of induced arrest in these patients have not been good in our hands

On the other hand, results of cardioplegia with potassium citrate in pediatric patients in general have been good, and we have used this

method about seventy five times In patients with congenital aortic stenosis we use it routinely and find it valuable particularly in a subaortic stenosis In all cases of aortic stenosis we have used a transaortic approach For calcific or acquired aortic stenosis we do not use potassium citrate arrest and depend upon a speedy valvulotomy to prevent serious myocardial ischemia

A word about retrograde perfusion of the coronary sinus is probably in order at this time We have used retrograde coronary perfusion in one case Ventricular fibrillation occurred immediately after the perfusion was started although the heart was doing well on the pump oxygenator up until that time

In the subsequent sixteen cases of aortic stenosis upon which we have operated, we have not used retrograde perfusion I raise the question of whether this method may be harmful rather than beneficial It seems possible to me at least that perfusion of a vein in the retrograde direction would predispose to the development of myocardial edema and ecchymosis

I would like to refer to our experience with ventricular septal defects We have used as cardioplegic agents both potassium citrate and acetyl choline Although we were enthusiastic about the method at first, during the past three months we have not used induced arrest in the ventricular septal defects for several reasons In the first place it usually requires an extra four minutes of perfusion Reducing the period of cardiopulmonary by pass will, I believe, reduce the number of complications after operation Induced arrest provides two advantages from a technical standpoint It makes the myocardium flaccid and easy to handle, and it makes it possible to stop coronary return Actually however the movement of the heart is not a signficant problem to the surgeon Furthermore, one can eliminate the return of blood through the coronary sinus by means of a temporary occluding clamp on the ascending aorta. Satisfactory repair can be done in a dry but slightly moving operating field the disadvantages and possible side effects produced by cardioplegic agents are thus eliminated. The possibility of trapping air in the left ventricle should be reduced by maintaining some myocardial tone throughout the procedure You will notice from Figure 190 that we now use an Ivalon patch sutured over the defect with a continuous suture For a number of technical reasons based upon our experience I believe this method gives the best results

A final point about cardioplegic agents which I believe is relevant to this discussion but which I have not heard mentioned at this meeting is the pH of these cardioplegic agents Recently Dr Abel Lazzarini at

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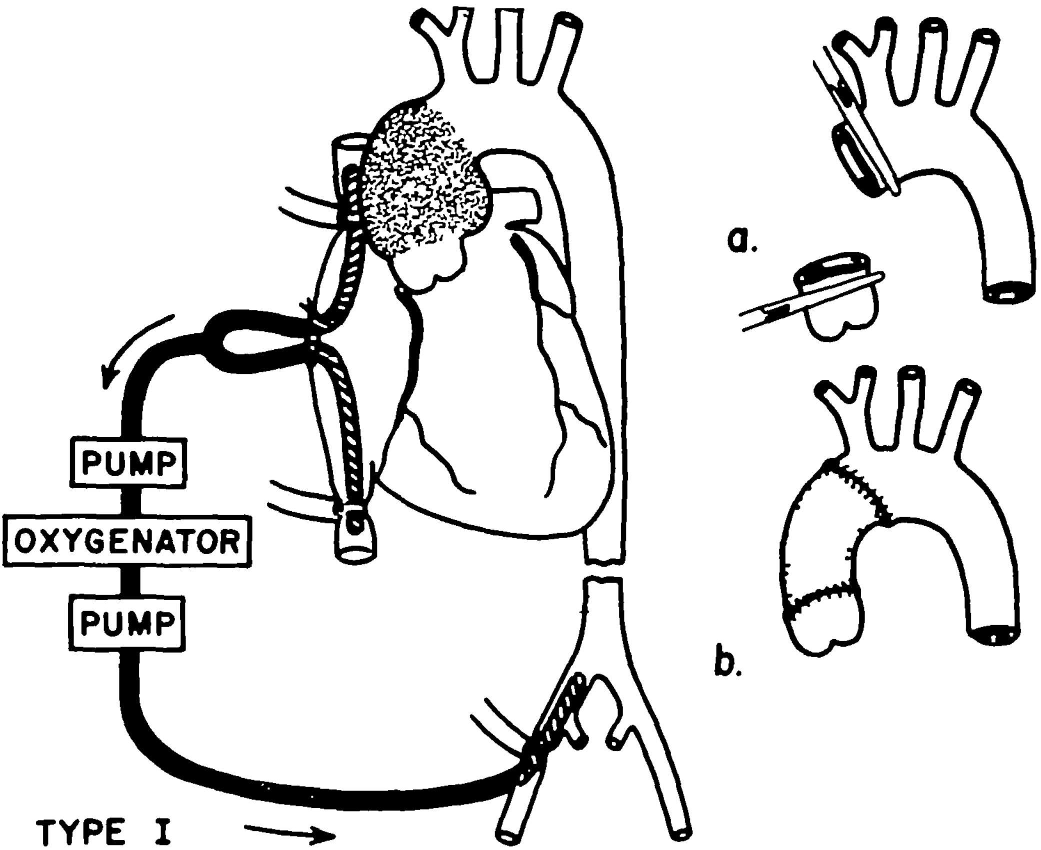


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uiotomy for otherwise recovery later may be difficult. Similarly when the clamp has been removed from the aorta it is wise to let a portion of the ventriculotomy bleed until a good strong beat returns—this permits escape of potassium and prevents myocardial stretching Manual com pression of the heart may be necessary to keep it small.

There are a number of questions which Dr Melrose might answer for us The first is whether the low pH of the potassium solution is of any significance the second is how he determined what dose should be used to produce elective arrest

Then lastly could he tell us of any experiments or thoughts he has had relative to the use of a continuous coronary artery perfusion through the base of the aorta with oxygenated blood and weak potassium concentration

DR. DENIS MELROSE San Francisco So much has gone by today that it would be very difficult to sum up adequately but I am sure you will agree that we can leave in the hands of people like Dr Bing and Dr Winterscheid the elegant problems of cardiac metabolism which are involved by our interference with heart action remembering with Dr Bentall that elective arrest merely reduces the rate of ischemic degeneration without eliminating it

In reference to drugs which will be used to stop the heart, it would seem that the choice has narrowed to acetylcholine or some longer acting variant, and potassium citrate acting as it does through the production of an ionic imbalance with elevation of potassium and re duction of calcium The type of arrest produced naturally differs but that they are both useful is obvious

I take exception to Dr Lam s film The reason is that it is too beauti ful and gives a false notion of the problem, which is only simple by illusion To do as beautiful an operation as he did requires considera ble personal skill, an effective and well tried perfusion system and much practice in the stopping of the heart Elective cardiac arrest carries considerable ethical problems and one must be very conscious of the practical difficulties which harass anybody working on this Theoretically it is perfectly safe and it can be so in practice but the moment you eliminate a natural mechanism which holds the heart muscle within a reasonable stretch length, you take the responsibility upon yourself of maintaining some adequate method for preventing any overstretch Difficulties arise from trapping of blood in any heart cavity Experiments which do not involve the opening and venting of the heart are I believe errors of practice, as perhaps is clamping of

New York University Post-Graduate Medical School made some comparative studies on pH of 2.5 per cent solution of Potassium Citrate and Potassium Chloride. Aqueous 2.5 per cent Potassium Citrate had a pH at 22°C of 6.92 and a similar solution of Potassium Chloride 7.45. I suppose acetylcholine has a pH similar to Potassium Chloride.

DR FRANK GERBODE, San Francisco: Before calling upon Dr Melrose I should like to make a few statements about elective arrest (which I believe is a better term than elective asystole or cardioplegia). Our experience in the laboratory and in thirty clinical applications during heart-lung by-pass has demonstrated that certain technical points should be observed. First, the potassium mixture should be injected rapidly; second, when there is a large heart, an aortic incompetence, a large bronchial arterial flow, or a patent ductus, it may require quite a lot of the solution to stop the heart, and this in turn may influence the speed with which the heart recovers. As arrest is being accomplished the heart will tend to fill with blood, thereby stretching the myocardial fibers. This is definitely to be avoided by quickly making the ventric-

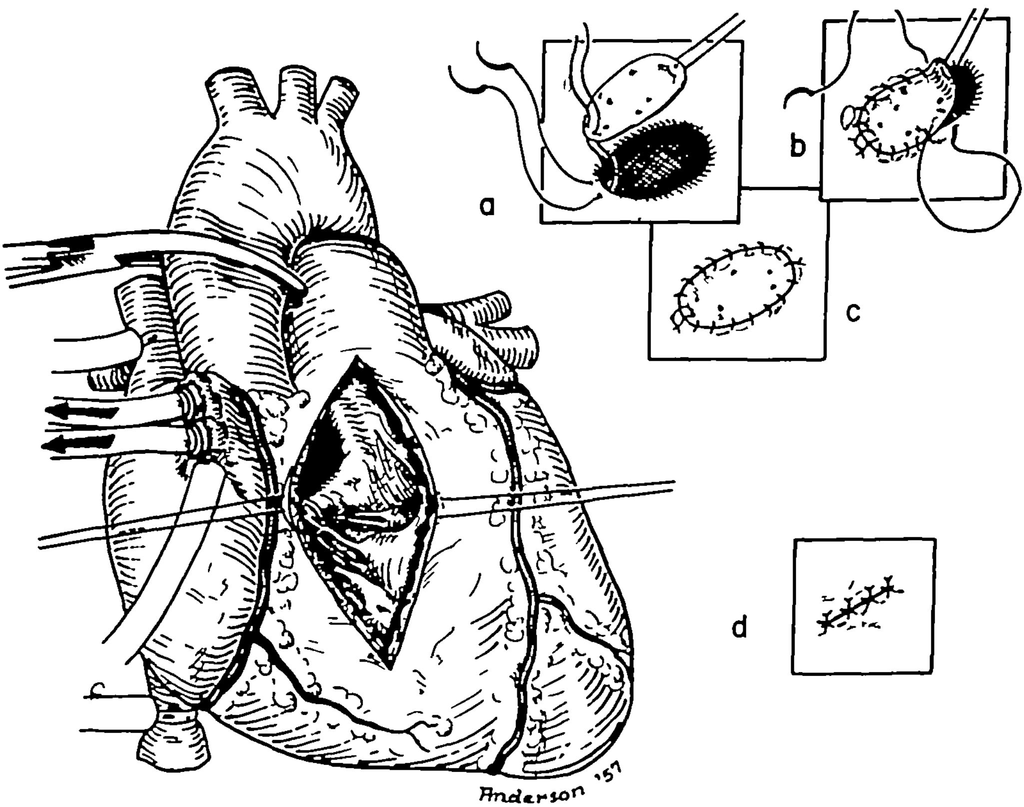


FIGURE 190

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Then lastly could he tell us of any experiments or thoughts he has had relative to the use of a continuous coronary artery perfusion through the base of the aorta with oxygenated blood and weak potassium concentration.

DR. DENIS MELROSE San Francisco So much has gone by today that it would be very difficult to sum up adequately but I am sure you will agree that we can leave in the hands of people like Dr Bing and Dr Winterscheid the elegant problems of cardiac metabolism which are invoked by our interference with heart action, remembering with Dr Bentall that elective arrest merely reduces the rate of ischemic degeneration without eliminating it

In reference to drugs which will be used to stop the heart, it would seem that the choice has narrowed to acetylcholine or some longer acting variant, and potassium citrate acting as it does through the production of an ionic imbalance with elevation of potassium and reduction of calcium. The type of arrest produced naturally differs but that they are both useful is obvious

I take exception to Dr Lam s film The reason is that it is too beautiful and gives a false notion of the problem, which is only simple by illusion To do as beautiful an operation as he did requires considerable personal skill, an effective and well tried perfusion system, and much practice in the stopping of the heart. Elective cardiac arrest carries considerable ethical problems and one must be very conscious of the practical difficulties which harass anybody working on this Theoretically it is perfectly safe and it can be so in practice but the moment you eliminate a natural mechanism which holds the heart muscle within a reasonable stretch length you take the responsibility upon yourself of maintaining some adequate method for preventing any overstretch Difficulties arise from trapping of blood in any heart cavity Experiments which do not involve the opening and venting of the heart are I believe errors of practice, as perhaps is clamping of

the pulmonary artery, where there may be a large bronchial blood flow All these problems have been brought out, but I feel it is my duty to define them If the heart at any time, from the beginning of arrest to a period after the heart has been restored to normal beating, is allowed to stretch, I think you are responsible for errors of technic

The pH of the solution you use is modified by the final concentration which is actually achieved within the heart muscle The arresting solution is injected into a cavity made up of the first portion of the aorta and the coronary vessels themselves Blood contained there further dilutes the potassium citrate solution Further, the aortic valve is not always competent at the moment of injection, nor is the heart always empty of blood and a further dilution from this source is likely Certainly in *our tests the pH of the solution actually reaching the heart was within* normal limits

The answer to the question why we chose this particular concentration is contained, of course, in the discussion of the pH Starting from the knowledge that to stop a heart effectively required a concentration of 1 mg of potassium citrate per milliliter of perfusate, an informed guess as to the dilution indicated that we should increase fifteen to twenty fold this concentration to insure an adequate level within the heart muscle No danger seemed to attend a high level, and in fact we were unable to determine the upper limit In the presence of aortic valvular incompetence or some communication between the aorta and the right side of the heart, as a ruptured sinus of Valsalva, this aspect of the problem becomes increasingly important

I have no evidence about the last question in clinical practice, but in isolated heart preparations a real prolongation of the time of arrest can be obtained by the intermittent perfusion through the coronaries of blood containing 2 5 mg of potassium citrate per milliliter If this is perfused for three to five minutes after each ischemic period of about fifteen minutes the isolated heart will be fully viable after three hours of complete arrest

I am afraid neither I nor my associates have had much success with retrograde coronary perfusion and feel that it involves even more difficulties than it solves

DR FRANCIS D MOORE, Boston Changing the subject, I would like to make one comment about the terminology of acidosis before we close Hypoxic acidosis is of course a form of metabolic acidosis We merely wish to emphasize that discrimination of this pathogenesis of metabolic acidosis may help in the future to distinguish

amongst the interplay of those many factors affecting the pH of patients on the pump-oxygenator There is nothing new about the concept of hypoxic acidosis In a sense the acidosis of the long-distance runner is hypoxic acidosis since it accumulates during a period of prolonged oxygen debt The concept is a fruitful one in pump oxygenator work and it emphasizes the importance of high flows

This is not to imply that other acidotic mechanisms are inactive We have seen some slides today showing high plasma chloride levels Dr John Perkins of Chicago has re-emphasized the occasional role of respiratory acidosis There may be many additional influences bearing on pH Respiratory acidosis in pump oxygenator physiology may result from very low flows with failure to wash out CO_2 from tissue sites This however seems to be very rare It is easier to wash out CO_2 than it is to oxygenate tissues under these circumstances Furthermore, in the oxygenator itself it appears to be easier to blow off CO_2 than it is to oxygenate For these reasons it would be my guess that true respiratory acidosis in these patients (indicated by a high pCO_2) is most often observed after they have been taken off of the pump and are faced with residual pulmonary pathology especially bronchopneumonia or inadequate ventilation of other causes

APPENDIX

PROCEEDINGS OF THE CONFERENCE

ON

Extracorporeal Circulation

SEPTEMBER 20, 21, 22, 1957

CHICAGO, ILLINOIS

Held under the auspices of the

SURGERY STUDY SECTION

NATIONAL INSTITUTES OF HEALTH

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Dr John D Stewart
Dr Henry Swan II

Dr Jack W Milder Executive Secretary

Subcommittee for Conference on Problems of Extracorporeal Circulation

Dr J Garrott Allen, Editor
Dr Francis D Moore, Chairman
Dr Andrew G Morrow
Dr Henry Swan II

This Conference was supported by a research grant H-3398 from the National Heart Institute, Public Health Service

COMMITTEE ON DEFINITION AND CONFORMITY OF NOMENCLATURE AND MEASUREMENTS USED IN STUDIES ON EXTRACORPOREAL CIRCULATION

COMMITTEE MEMBERS

CHAIRMAN FRANK L A GERBODE, Stanford Medical School, San Francisco, California
HENRY T BAHNSON, The Johns Hopkins Hospital, Baltimore, Maryland
HUGH H BENTALL, Hammersmith Hospital, London, England
LELAND C CLARK, JR , Antioch College, Yellow Springs, Ohio
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DENIS G MELROSE, University of London, England and Stanford Medical School, San Francisco, California
JOHN F PERKINS, JR , University of Chicago, Chicago, Illinois
ELTON WATKINS, JR , Children's Medical Center, Boston, Massachusetts

IN THE INTEREST of uniformity and common understanding the Surgical Study Section believes that some standardization of terms used in extracorporeal circulation is desirable, and therefore appointed a committee to prepare suggestions with these purposes in mind The suggestions offered should neither be considered complete nor final, but perhaps only a step towards the development of a language which might facilitate publication and scientific presentation of subject matter in this field

No better examples could be chosen to illustrate the need for standardization than is provided by the measurement of vascular pressures and flows, by the determination of the efficiency of pump oxygenators, or by the problems underlying respiratory exchange

Pressures and Flows It is desirable to document in publications the type of pressure recording system used including the type and model number of the manometer, the direct writer, and the diam-

eter and length of fluid channels connecting the manometer to the vascular system These data may be placed conveniently in a foot note in the methods section of the paper Where interpretation of pulse contours is crucial to development of the author s thesis publication of representative original tracings is desirable

Types of Pressures Recorded A number of recording conditions should be reported in publications These include a description of the position of the recording cannula in relation to the direction of blood flow (*end or side* pressure) whether a mean or pulse contour tracing is made and the zero reference point

End Arterial Pressure Where the term "end pressure" is used in relation to an anatomic position in the arterial tree it refers to a pressure measurement made with the manometer cannula in the proximal end of a divided vessel directed upstream toward the heart. This term should not be confused with the term "end diastolic pressure" which has a different meaning in atrial pressure measurements (see below)

Side Pressure The manometer cannula is placed in the side of the unobstructed vessel so that the orifice of the manometer system is parallel to the direction of unimpeded blood flow End arterial pressures may be somewhat higher than simultaneous side pressures due to a water hammer effect of blood striking the manometer in the end position

Pulse Contour The *pulse contour* or *pressure pulse* measurement is made with a manometer system responding fast enough to reproduce quick pressure fluctuations within the vascular bed Manometer systems having very small fluid displacements must be used to give a satisfactory frequency response The term *pressure pulse* refers to the contour characteristics of the entire pulse while the term *pulse pressure* means the pressure difference between systolic and diastolic pressure

Systolic Pressure Peripheral arterial measurements of systolic pressure (such as end femoral arterial pressure recording) may be considerably higher than central arterial systolic pressure due to the conversion of energy stored in the moving blood into pressure energy when flow is stopped at the closed end of the vessel or in the needle in the vessel (water hammer effect) The disparity may be accentuated in abnormal vasomotor states occurring with

hypovolemia or with low systemic blood flow Conclusions concerning central arterial systolic pressure derived from peripheral recordings must be tentative and rough

Diastolic Pressure: In the arterial pressure tracing, diastolic pressure is registered just prior to the upward deflection of rapid ventricular ejection Diastolic pressure within the atrial chamber is measured just prior to the vibration caused by closure of the atrioventricular valve (the C wave) This pressure value has been called variously the *end diastolic pressure* or the *Z pressure* In critical atrial pressure analyses, one cannot compare the end diastolic pressure measurement to mean atrial pressure (obtained by integration of the atrial pulse through an entire cardiac cycle) until it can be shown that the wave of atrial systolic contraction or waves due to incompetency of the atrioventricular valves introduce a negligible difference between the atrial mean pressure and atrial end diastolic pressure In any event the worker should describe just what is meant by atrial pressure values, whether it is an *end diastolic pressure*, determined by inspection of the pulse contour tracing, or a *mean atrial pressure*, obtained by integration of the entire atrial pulse contour

Mean pressure cannot be obtained by averaging systolic and diastolic pressures but must be obtained by averaging each and every instantaneous pressure prevailing within the pulse cycle A pressure pulse with a short high peak of systole and a prolonged diastole would have a mean pressure close to the diastolic value rather than a value half-way between the systolic and diastolic figures In the past it was necessary to measure the area beneath the pulse contour with a mechanical device and divide by the pulse cycle time to obtain the mean pressure value Now, it is possible to obtain the smoothing (or integrating) effect by damping out the pressure variations electronically with suitable circuits so that the direct writer traces the mean pressure value This gives the mean pressure for the entire heart cycle One must resort to the older graphic methods if the components of *mean systolic pressure* and *mean diastolic pressure* are desired To obtain a valid mean tracing, the worker must first assure himself that the basic pulse contour, from which the electronic mean value is to be obtained, is free from artifacts

Differential Pressure Measurements Under certain circum-

stances a recording is made of a pressure value which is the difference between two actual pressures Special manometers may be utilized which directly measure such pressure differences In the absence of a differential manometer multiple points on carefully-calibrated primary curves may be subtracted to reconstruct the differential pulse measurement The flow meters which utilize the principle of pressure drops across a constriction require differential pressure measurements

Another example of a differential pressure is the *effective atrial pressure* obtained by comparing the pressure within the atrium in the intact chest against the subatmospheric intrapleural pressure just outside the heart wall thereby correcting atrial pressure values for variations in the sub-atmospheric intrapleural pressure Variations in sub atmospheric intrapleural pressure may be striking during hypovolemia

Little attention has been paid in surgical studies to this source of error in comparing atrial pressure measurements made during cardiac catheterization with the chest intact with studies made with the chest open during surgery when the pressure surrounding the heart is atmospheric

Specificity Concerning the Point of Measurement of Pressure The point at the vascular system should be specified where the pressure is measured, e g the artery from which pressure was measured should be indicated rather than the loose description "arterial pressure" Similar precision is necessary in the venous system, where pressure measured in peripheral veins may not accurately reflect central venous pressure as measured within the right atrium The convention of pressure measurements within the pump oxygenator should include documentation of *Input Line Pressure* for pressure within the line passing blood from the subject to the pump or pump-oxygenator and *Output Line Pressure* for those measurements in the line passing blood back to the subject from the mechanical device The zero reference level for line pressure measurement may vary considerably from the standard zero reference level for intravascular pressure measurements (see below) since the line pressure measurements are made for purposes which have no direct relationship to intravascular pressure measurements or reference levels

Zero Reference Levels It is desirable to specify the zero refer

ence level of pressure measurements in relation to the patient's position on the operating table Appreciable errors may result if careful correction to a standard reference zero level is not carried out in atrial pressure measurements or in hypotensive arterial observations Although we recognize that several different methods of standardization are equally satisfactory, we recommend that standard reference zero levels be adopted in the bypass field for purposes of uniformity

(a) supine child 5 cm above the table top
(b) supine adult 10 cm above the table top
(c) supine dog 10 cm above the table top
(d) human in the lateral decubitus Fifth thoracic spinous process
(e) dog in the lateral decubitus Fifth thoracic spinous process

FLOW MEASUREMENTS

Cardiac bypass surgery is in such a dynamic state now that it is useless to try to define such terms as "ideal flow," "high flow," and "low flow" Such definitions would become historical curiosities within a short time after publication of this report However, certain techniques and expressions might be clarified to aid in accurate communication in the field At the present time, considerable data on bypass flows are being presented without specific mention of the manner in which the flow figure was determined It would be desirable to follow certain conventions in measuring and reporting such measurements

(a) Where the ideal situation of continuous monitoring of flow during the actual bypass procedure can be carried out by flowmeter, the accuracy of flowmeter calibrations and stability should be stated
(b) Where the flow is determined by preliminary calibration of flow rate at a given pump rate setting, the preliminary calibration should be carried out with the actual cannula system to be used in the bypass in position and against a specific pressure head simulating the arterial pressure against which the pump system must work during the by-

pass. This is easily done if the arterial cannula orifice connected to the output line is elevated above the pump a distance equivalent to the pressure head desired during the calibration run. In gravity drainage pump-oxygenators where the pump may be a considerable distance below the operating table, this pressure head elevation must be added to the distance the line is elevated to reach the operating table.

Assuming that 1.36 cm. of water in the arterial line is equivalent to 1.0 mm. of mercury, the following heights produce common pressure heads:

Pressure Head Mm. Hg	*Height (Inches)*	*Height (Cm.)*
25	13.4	34
50	26.8	68
75	40.3	102
100	53.7	136
125	67.1	170
150	80.3	204
175	93.0	238
200	107.4	272

(c) Published descriptions of flow should include the absolute volume of flow expressed in liters per minute, and the flow in ml. per minute per kilogram body weight or flow in liters per minute per square meter of body surface area. The expression of flow on the basis of body surface area is preferable to the weight expression since it more precisely equates flow to metabolic demand in the younger age groups. A chart derived from the DuBois nomogram is published.

Recently extensive studies of energy metabolism of premature and newborn infants have been carried out by Scandinavian workers.

Analysis of these data indicates that the chart may be used as a parameter of metabolic activity in such special pediatric groups. In studies on dogs, body surface area may be computed using a formula based upon weight:

$$\text{BSA in } M^2 = 0.112\sqrt{(\text{weight kg})}$$

Weight Kg	*BSA M²*	*Weight* Kg	*BSA M²*	*Weight* Kg	*BSA M²*	*Weight* Kg	*BSA M²*
1	0 112	11	0 56	21	0 85	31	1 11
2	0 178	12	0 59	22	0 88	32	1 13
3	0 233	13	0 62	23	0 90	33	1 15
4	0 282	14	0 65	24	0 93	34	1 18
5	0 327	15	0 68	25	0 96	35	1 20
6	0 37	16	0 71	26	0 98	36	1 22
7	0 41	17	0 74	27	1 01	37	1 24
8	0 45	18	0 77	28	1 03	38	1 27
9	0 49	19	0 80	29	1 06	39	1 29
10	0 52	20	0 83	30	1 08	40	1 32

Infrequently, dogs of odd length should have surface area computation on the basis of equations including corrections for nose to tail-base length, L (measured along the ventral surface of the trunk)

$$BSA \text{ in } M^2 = 0\ 2864 \text{ Wt Kg } \ 0\ 367 \text{ L (in meters)}$$

No data exist to indicate the degree of correlation between surface area and metabolic demand in small puppies.

Definition of Various Terms Utilized in Describing the Properties of Flow: A number of terms should be defined since they are utilized frequently in reports of bypass procedures

Non-pulsatile Flow. Currently-existing models of the roller-type pumps giving so-called non-pulsatile flow all induce a degree of pulsation into the flow pattern as successive rollers enter the platen of the pump It would be best to reserve the term *non-pulsatile flow* for truly continuous streams, such as those derived from gravity flow bottles The roller pumps of the DeBakey type give flow which is best described as *Low Amplitude Pulsatile Flow*

High Amplitude Pulsatile Flow. Conversely pumps of the Dale-Schuster type give pulses of high amplitude

***Mean and Instantaneous Flow*·** Where the flow computation is based upon observation of the accumulation of a volume of fluid in a reservoir bottle over a measured time interval, a *mean flow* value is being obtained *Instantaneous flow* values are obtained by the use of rapidly-responding flowmeters which permit the graphic registration of cyclical variations of flow rate during successive phases of the cardiac cycle

FLOW RESISTANCE OBSERVATIONS

The concepts of resistance to flow are important to the surgeon not only in permitting evaluation of his pump-oxygenator so that efficient design may improve mechanical efficiency and lessen blood trauma but also in precisely documenting the changes within the diseased vascular system which impede the flow of blood Such obstructions may be in the nature of valvular constrictions or changes of small vessel bore due to vessel wall changes or alterations of vasomotor tone

Definition of Resistance The term *resistance* denotes opposition to the flow of a fluid Arithmetically it is simply the pressure required to produce a given flow or Resistance = Pressure/Flow Thus if a high pressure say 200 mm Hg is required to produce 1 liter of blood flow per minute the resistance would be twice as great as if only 100 mm were required

Diameter of the minute blood vessels chiefly the arterioles is a primary factor affecting resistance Changes in the viscosity of the blood due to variations in concentration of the plasma proteins and to a much greater extent, in red cell count, also affect resistance to flow a classical example being the sluggish flow seen in polycythemia

Various Types of Resistance Expressions The most common resistance expression used in physiological discussions is the value of *Total Peripheral Resistance* This is an indication of the resistance to the flow of blood prevailing generally in the vascular system The term is applied only to the systemic circulation (A comparable value in the pulmonary circuit is commonly called the *pulmonary resistance* but would better be called the *pulmonary vascular resistance* to indicate that it is a measure of circulatory conditions within the lung) The *total peripheral resistance* is derived from the resistances which prevail within vascular beds of the various organs and tisues Since the circulation is connected in a parallel circuit with organs deriving blood supply from branches of the aorta the *total peripheral resistance* is less than any given territorial resistance through an organ Moreover changes in resistance in certain organs may be compensated for by opposite resistance changes in other organs without a change in total peripheral resistance or arterial blood pres

Weight Kg	*BSA M²*	*Weight* Kg	*BSA M²*	*Weight* Kg	*BSA M²*	*Weight* Kg	*BSA M²*
1	0.112	11	0.56	21	0.85	31	1.11
2	0.178	12	0.59	22	0.88	32	1.13
3	0.233	13	0.62	23	0.90	33	1.15
4	0.282	14	0.65	24	0.93	34	1.18
5	0.327	15	0.68	25	0.96	35	1.20
6	0.37	16	0.71	26	0.98	36	1.22
7	0.41	17	0.74	27	1.01	37	1.24
8	0.45	18	0.77	28	1.03	38	1.27
9	0.49	19	0.80	29	1.06	39	1.29
10	0.52	20	0.83	30	1.08	40	1.32

Infrequently, dogs of odd length should have surface area computation on the basis of equations including corrections for nose to tail-base length, L (measured along the ventral surface of the trunk)

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Mean and Instantaneous Flow. Where the flow computation is based upon observation of the accumulation of a volume of fluid in a reservoir bottle over a measured time interval, a *mean flow* value is being obtained *Instantaneous flow* values are obtained by the use of rapidly-responding flowmeters which permit the graphic registration of cyclical variations of flow rate during successive phases of the cardiac cycle

the pressures necessary at the upstream end of a plastic tube The types of flow may be estimated by measurements of pressure gradients in the system or may be roughly predicted by computations involving the diameter of the tube and velocity of flow Tremendous pressure heads may be required to propel adequate volumes of blood through long narrow tubes or cannulas since the laws of resistance require that the pressure varies geometrically with tube diameter for a given flow, linearly with length if flow is laminar and geometrically with length if turbulent flow conditions prevail Irregular orifices and unnecessary constrictions enhance these effects

It should be emphasized that regular consultations with biophysicists and engineering experts are most useful in the avoidance of pitfalls in this complex field Considerable engineering knowledge exists concerning the flow of fluids in tubes Although many of the engineering formulae cannot be used directly due to imperfections in our knowledge of blood flow approximations and the exchange of concepts can prove most valuable

Efficiency of Pump-Oxygenators: The problem of critical evaluation of the relative efficiency of oxygenator units necessitates precise expression of ideas involved and therefore standardized terminology

The following terms appear to be useful

"By pass circulating volume" is that volume of blood in the entire circuit outside the body of the subject while the heart lung by pass is fully supporting the circulation of the subject.

"Priming volume" is that volume of blood necessary in the entire circuit outside the body of the subject to run the apparatus at a minimal flow rate

"Hold up" is the increment of blood it is necessary to add to the priming volume in order to reach the by pass circulating volume needed to provide the flow rate required for the subject of the moment.

Therefore priming volume + hold up = by pass circulating volume

"Stand by volume" is that amount of blood it is necessary to hold in reserve for safe operation of the heart lung by pass

In expressing the performance of a given by pass apparatus the

sure This may result in a change of the partition of blood flow Commonly, such conditions obtain when systemic blood flow is low due to shock Such organs as the kidney undergo a vasoconstrictive increase in resistance to preserve the total peripheral resistance and blood flow to more essential organs A reciprocal fall in vasomotor resistance may occur in the more vital organ Understanding of this method of total body homeostasis is crucial in pump-oxygenator work since an excessively low perfusion may result in organ ischemia despite adequate arterial pressure levels That the vasoconstricted organ may survive after such ischemia during short periods of by-pass does not necessarily indicate the extent of the injury to it and its ability to survive longer periods of ischemia as our methods of bypass increase in complexity Indications of organ status, such as electro-encephalographic tracings, acid-base studies, and renal function studies, become important to us as we extend the periods of bypass

Regional organ resistance and the partition of perfusion may have special properties during heart-lung bypass since the propelling blood forces are introduced into an unnatural point of the aortic system It is well-known that cerebral blood flow is aided by the centrifugal forces which throw blood into the carotid arteries as the ventricular content is ejected into the curve of the aortic arch Studies are indicated to show whether or not a somewhat different partition of organ flow prevails, at the expense of cerebral blood flow, when pulsations of low amplitude force blood through the left subclavian artery into distal aorta directed away from the aortic arch

Significance of Resistance Concepts in the Design of Pump-Oxygenators. Basic understanding of resistance concepts is useful in oxygenator design It is reasonable to assume that minimal resistance to flow within the mechanical device results in a lower pressure being developed in its channels, and this lower pressure is gentler to the blood Quantification of the pressure-flow effects can prove useful in achieving this end The pressure fall in a fluid system flowing in a tube varies linearly with the length of the tube so long as the flow is laminar The pressure gradient varies geometrically with length when flow is turbulent Avoidance of turbulent flow consequently would prove useful in minimizing

which the subject would otherwise occupy All cannula orifices should be firmly fixed below the surface of the reservoir to prevent whipping and bubbles and the volume of fresh blood in the entire circuit to be standard should be two times the by pass circulating volume Blood should be freshly drawn and have a Hgb of 14 gm per cent or more it should be maintained at 37° and undiluted in the circuit The flow rate should be maximal

The provided data on hemolysis to be adequate should include

1) "Index of hemolysis" = added grams of free Hgb per 100 liters pumped
2) Final plasma Hgb concentration

It does not seem inappropriate to furnish data on heart lung by pass procedures in addition and in this context the following are suggested

GENERAL TERMS

1 "Heart lung bypass "
   A term used to describe the condition existing when artificial heart and lungs are being used to maintain the circulation
2 "Extracorporeal Circulation "
   A general term used for a system employing a circulation outside the body
3 "Duration by pass" should be qualified as follows
   Time of a caval occlusion
   b partial pump dependency
   c complete pump dependency
4 "Elective Cardiac Arrest "
   Suggested as a simpler term than "cardioplegia" or induced cardiac asystole "

Respiratory Exchange The development of extracorporeal circulation has involved contributions from a variety of scientific disciplines and it can be lauded as an advance in medicine that this is the case It is suggested that adoption of an already accepted system of definitions and symbols may enhance this exchange of ideas and knowledge

following data, obtained while a specific animal or patient with Hgb 14 gm % or more is supported in a steady state by that apparatus, appear to be essential

1) Arterial pH
2) Composition of the oxygenating atmosphere
3) Temperature of oxygenator
4) Venous per cent Hgb saturation (or O_2 content)
5) Arterial per cent Hgb saturation (or O_2 content)
6) By-pass circulating volume
7) Priming volume
8) Flow rate of blood to the subject
9) Ml O_2 added per minute by the oxygenator

Simple comparisons of heart-lung by-pass units are possible by the following three factors

1) Maximal flow rate possible
2) Ratio of minute flow to by-pass circulating volume
3) Gas exchange ratio $\dfrac{100 \times (\text{ml } O_2 \text{ added per minute})}{\text{ml by-pass circulating volume}}$

with maximal flow rate and otherwise the conditions described above, an A-V difference of at least 5 vol %, and an arterial oxygen saturation of at least 95%

Hemolysis proper is not a problem of cardinal importance in most currently known by-pass machines It is a valuable index, however, of the amount of trauma inflicted upon the blood, trauma which may be a factor in as yet poorly understood damage to the subject A standard test for the hemolytic effect of by-pass should exclude the subject, who may remove much hemoglobin from the plasma It should include in the circuit the arterial and venous cannulae and all tubing utilized in by-pass, for hemolysis is more marked in areas of constriction and turbulence than in areas of smooth flow It should pump against a pressure equal to the usual subject aortic pressure during by-pass, for several pumping mechanisms in current use contribute a measure of mechanical shock in the propulsion of blood against pressure

It is suggested that an assembly permitting ready comparison might consist of a reservoir at a level of 140 cm higher than that

"S" = Saturation in per cent Defined as $100 \times O_2$ content of hemoglobin/O_2 capacity of hemoglobin Dissolved oxygen is excluded

2 Small capital letters are used to define the location of a gas in the respiratory tract Thus "I" "E" and "A" refer respectively to inspired expired and alveolar gases

3 Lower case letters are used to localize a gas combined with or dissolved in blood Thus "a" and "v" refer respectively to arterial and venous blood the exact location to be specified $\bar{v}$ refers to mixed venous blood

4 The full chemical symbol in small capital letters is used to designate the type of gas and appears as a subscript if following the symbols given in paragraphs 1-3 above

5 If used together the variables follow one another in the order given in paragraphs 1-4

Examples P_{aO_2}, $P_{\bar{v}O_2}$ = partial pressure of oxygen in arterial and mixed venous bloods respectively

$\dot{V}_{O_2}$ = ml oxygen consumed per minute C_{aO_2}, $C_{\bar{v}O_2}$ = concentration (content) of oxygen in ml/100 ml blood in arterial and mixed venous bloods respectively Both oxygen combined with hemoglobin plus dissolved oxygen is meant when referring to concentration or content thus arterio venous oxygen content difference = $C_{aO_2} - C_{\bar{v}O_2}$

$\dot{Q}c$ = blood flow in ml or L/min through the pulmonary capillaries (c)

Therefore the equation for cardiac output as defined by the Fick principle is

$$\dot{Q}c = \frac{\dot{V}_{O_2}}{C_{aO_2} - C_{\bar{v}O_2}}$$

The Committee which in 1950 formulated the Standardization of Definitions and Symbols in Respiratory Physiology state that New symbols are easily added to the list without altering the method of symbolization The widespread present use of pump—oxygenators may call for such additions For example $\dot{Q}e$ c might refer to the volume flow of blood in liters min through the external pump or pump—oxygenator circuit and S_{IO_2} and S_{OO_2} to oxygen saturation in input line I (venous) and outflow line

Use of a standardized set of definitions and abbreviations for the gaseous constituents, namely, oxygen, carbon dioxide, and nitrogen of blood should facilitate communication in publications and scientific meetings concerned with pump-oxygenators. Fortunately, a uniform system was adopted in 1950* in a field closely associated with cardio-vascular surgery, namely cardio-pulmonary physiology, and has subsequently been applied on a wide scale in publications dealing with clinical applications of physiology.†‡ A few of the definitions and symbols from the original article are included here because of their relevance to the use of pump-oxygenators.

1. General variables are represented by large capitals, as for example

"V" = gas volume. Pressure, temperature and whether dry or saturated with water vapor should be stated.

For measurements of oxygen uptake or consumption, volumes of O_2 should be expressed as "Standard Temperature and Pressure, Dry" (STPD), i.e. at 0°C, 760 mm pressure, gas dry. For measurements of volumes of gas exhaled, volumes are expressed as "Body Temperature and Pressure, Saturated" (BTPS) i.e. at 37°C, existing barometric pressure, saturated with water vapor, which will exert a vapor tension of 47 mm Hg at that temperature. When gases are collected in a spirometer or Douglas bag, they are at Ambient (room) Temperature and Pressure, Saturated (ATPS) and the volume must always be corrected to STPD or BTPS by a suitable equation.

"Q" = Volume of blood in ml or L. A dot over a letter means per unit time, usually 1 minute, thus

"V" = gas volume/min

"Q" = Volume flow of blood, in ml/min or L/min, as specified

"P" = Partial pressure of a gas, in mm Hg

"C" = Concentration or content of a gas in ml/100 ml blood

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* Standardization of Definitions and Symbols in Respiratory Physiology. *Fed Proc*, 9 602, 1950.

† Comroe, J. H. *The Lung*. Clinical Physiology and Pulmonary Function Tests. Chicago, The Year Book Publishers, 1955. 219 pp.

‡ Zimmerman, L. M. and Levine, R. *Physiologic Principles of Surgery*. Philadelphia, W. B. Saunders Company, 1957. 988 pp.

"S" = Saturation in per cent. Defined as 100 × O_2 content of hemoglobin/O_2 capacity of hemoglobin. Dissolved oxygen is excluded.

2. Small capital letters are used to define the location of a gas in the respiratory tract. Thus "I," "E" and "A" refer respectively to inspired, expired and alveolar gases.
3. Lower case letters are used to localize a gas combined with or dissolved in blood. Thus "a" and "v" refer respectively to arterial and venous blood, the exact location to be specified. $\bar{v}$ refers to mixed venous blood.
4. The full chemical symbol in small capital letters is used to designate the type of gas and appears as a subscript if following the symbols given in paragraphs 1-3 above.
5. If used together, the variables follow one another in the order given in paragraphs 1-4.

Examples: Pa_{O_2}, $P\bar{v}_{O_2}$ = partial pressure of oxygen in arterial and mixed venous bloods respectively.

$\dot{V}_{O_2}$ = ml oxygen consumed per minute. Ca_{O_2}, $C\bar{v}_{O_2}$ = concentration (content) of oxygen in ml/100 ml blood in arterial and mixed venous bloods respectively. Both oxygen combined with hemoglobin plus dissolved oxygen is meant when referring to concentration or content; thus arterio-venous oxygen content difference = $Ca_{O_2} - C\bar{v}_{O_2}$.

$\dot{Q}c$ = blood flow in ml or L/min through the pulmonary capillaries (c).

Therefore the equation for cardiac output as defined by the Fick principle is

$$\dot{Q}c = \frac{\dot{V}_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}}$$

The Committee which in 1950 formulated the Standardization of Definitions and Symbols in Respiratory Physiology state that "New symbols are easily added to the list without altering the method of symbolization. The widespread present use of pump-oxygenators may call for such additions. For example, $\dot{Q}ec$ might refer to the volume flow of blood in liters/min through the external pump or pump-oxygenator circuit and Si_{O_2} and So_{O_2} to oxygen saturation in input line (i) (venous) and outflow line

"o" (arterialized) Corresponding partial pressures and contents of oxygen and carbon dioxide in these lines would be "P_{IO_2}", "P_{oO_2}", "C_{IO_2}" and "C_{oO_2}"

It will be noted that the conventions outlined in paragraphs 1-5 above have been followed in these examples

Eventually, a set of symbols such as these or similar ones devised specifically for use with pumps or pump—oxygenators may be agreed upon and then standardized Their use should provide advantages similar to those already obtained in cardiopulmonary physiology, requiring only to be defined once, the brief symbol alone thereafter being used in both text and tables